GEORGE C. GORDON LIBRARY

WORCESTER POLYTECHNIC INSTITUTE
Worcester, Massachusetts 01609

ADVANCED ORGANIC CHEMISTRY:
REACTIONS, MECHANISMS, AND STRUCTURE

McGRAW-HILL SERIES IN ADVANCED CHEMISTRY

Senior Advisory Board W. CONARD FERNELIUS LOUIS P. HAMMETT
HAROLD H. WILLIAMS

Editorial Board DAVID N. HUME GILBERT STORK
EDWARD L. KING DUDLEY R. HERSCHBACH JOHN A. POPLE

AMDUR AND HAMMES *Chemical Kinetics: Principles and Selected Topics*
BAIR *Introduction to Chemical Instrumentation*
BALLHAUSEN *Introduction to Ligand Field Theory*
BENSON *The Foundations of Chemical Kinetics*
BIEMANN *Mass Spectrometry (Organic Chemical Applications)*
DAVIDSON *Statistical Mechanics*
DAVYDOV *(Trans. Kasha and Oppenheimer) Theory of Molecular Excitons*
DEAN *Flame Photometry*
DJERASSI *Optical Rotatory Dispersion*
ELIEL *Stereochemistry of Carbon Compounds*
FITTS *Nonequilibrium Thermodynamics*
FRISTROM AND WESTENBERG *Flame Structure*
HELFFERICH *Ion Exchange*
HILL *Statistical Mechanics*
HINE *Physical Organic Chemistry*
JENSEN AND RICKBORN *Electrophilic Substitution of Organomercurials*
KAN *Organic Photochemistry*
KIRKWOOD AND OPPENHEIM *Chemical Thermodynamics*
KOSOWER *Molecular Biochemistry*
LAITINEN *Chemical Analysis*
MCDOWELL *Mass Spectrometry*
MANDELKERN *Crystallization of Polymers*
MARCH *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*
MEMORY *Quantum Theory of Magnetic Resonance Parameters*
PITZER AND BREWER *(Revision of Lewis and Randall) Thermodynamics*
POPLE, SCHNEIDER, AND BERNSTEIN *High-resolution Nuclear Magnetic Resonance*
PRYOR *Free Radicals*
PRYOR *Mechanisms of Sulfur Reactions*
RAAEN, ROPP, AND RAAEN *Carbon-14*
ROBERTS *Nuclear Magnetic Resonance*
ROSSOTTI AND ROSSOTTI *The Determination of Stability Constants*
SIGGIA *Survey of Analytical Chemistry*
SOMMER *Stereochemistry, Mechanisms and Silicon*
STREITWIESER *Solvolytic Displacement Reactions*
SUNDHEIM *Fused Salts*
WIBERG *Laboratory Technique in Organic Chemistry*

Advanced Organic Chemistry: Reactions, Mechanisms, and Structure

JERRY L MARCH

Professor of Chemistry,
Adelphi University

McGRAW-HILL BOOK COMPANY

New York St. Louis San Francisco Toronto London Sydney

Advanced Organic Chemistry:
Reactions, Mechanisms, and Structure

Copyright © 1968 by McGraw-Hill, Inc. All Rights Reserved. Printed in the United States of America. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior written permission of the publisher.

Library of Congress Catalog Card Number 67-16932

07-040240-x

6 7 8 9 10 11 KPKP 7 9 8 7 6 5 4 3 2

QD
251
M17

128625

For **BEVERLY, GALE, DAVID,** *and* **JUNE**

Preface

This book has grown out of a graduate course in advanced organic chemistry which I have been teaching at Adelphi University for a number of years. It is thus designed for students who have taken the standard one-year undergraduate organic and physical chemistry courses. I have attempted to give equal weight to the three fundamental aspects of the study of organic chemistry: reactions, mechanisms, and structure. A student who has completed a course based on this book should be able to approach the literature directly, with a sound knowledge of modern basic organic chemistry. I have treated lightly, or not at all, the major special areas of organic chemistry: terpenes, carbohydrates, photochemical and electrochemical reactions, steroids, and the like. It is my opinion that these topics are best approached after the first year of graduate study, when the fundamentals have been mastered, either in advanced courses, or directly, by consulting the many excellent books and review articles available on these subjects.

I have organized the material differently from that of most first-year organic textbooks. With a few exceptions, undergraduate organic chemistry is taught on the basis of functional groups: the student is introduced one at a time to the methods of preparation and the reactions of alcohols, ethers, carboxylic acids, etc. Mechanisms are taken up as the reactions are encountered. This is an appropriate way to teach a first course in organic chemistry, since it does not overwhelm the student with too much material too soon. However, for a *second* course, an arrangement based on reaction types is sounder. Since the student has already learned the *language* of organic chemistry, he is prepared to be shown that, despite the large number of organic reactions, a relatively few principles suffice to explain nearly all of them. Accordingly, the reactions-mechanisms section of this book (Part 2) is divided into 10 chapters, each concerned with a different type of reaction. In the first part of each chapter the appropriate basic mechanisms are discussed along with considerations of reactivity and orientation, while the second part consists of numbered sections devoted to individual reactions, where the scope and the mechanism of each reaction are discussed. I have used numbered sections for the reactions, because I have found that students learn better when they are presented with clear outlines (for a further discussion of the arrangement of Part 2, see pp. 247–249). Since the methods for the preparation of individual classes of compounds (e.g., ketones, nitriles, etc.) are not treated all in one place, an index has been provided (Appendix C) by use of which all methods for the preparation of a given type of compound will be found. At first, I had hoped to provide an actual example, from the literature, for each reaction discussed. However, the space required would have been too great. In partial compensation, I have included, for each reaction, a list of all *Organic Syntheses* references. Thus for most reactions the student can consult actual examples in *Organic Syntheses.*

The structure of organic compounds is discussed in the first six chapters of Part 1. This section provides a necessary background for the understanding of mechanisms, and is also important in its own right. The discussion begins with chemical bonding, proceeds through stereochemistry, and ends with a chapter on instrumental methods used to determine structure. Part 1 concludes with three chapters which give further background to the study of mechanisms.

In addition to reactions, mechanisms, and structure, the student should have some familiarity with organic nomenclature and with the literature of organic chemistry. Chapters devoted to these topics have been placed in the appendix, though many teachers may wish to cover this material at the beginning of the course.

In treating a subject as broad as the basic structures, reactions, and mechanisms of organic chemistry, it is obviously not possible to cover each topic in great depth. Nor would this be desirable even if possible. Nevertheless, students will often wish to pursue individual topics further. An effort has therefore been made to guide the reader to pertinent review articles and books published since about 1950. In this respect, this book is intended to be a guide to the secondary literature (since about 1950) of the field it covers. Furthermore, in a graduate course, students should be encouraged to consult primary sources. To this end I have included about 3,000 references to original papers.

Although basically designed for a one-year course on the graduate level, this book can also be used in advanced undergraduate courses, as long as they are preceded by one-year courses in organic and physical chemistry. It can also be adapted, by the omission of a large part of its contents, to a one-semester course. Indeed, even for a one-year course, more is included than can be conveniently covered. Many individual sections can be easily omitted without disturbing continuity.

The reader will observe that this text contains much material which is included in first-year organic and physical chemistry courses, though in most cases it goes more deeply into each subject and, of course, provides references which first-year texts do not. It has been my experience that students who have completed the first-year courses often have a hazy recollection of the material, and greatly profit from a re-presentation of the material, if it is organized in a different way. It is hoped that the organization of the material on reactions and mechanisms will greatly aid the memory and the understanding. In any given course the teacher may want to omit some chapters because his students already have an adequate knowledge of the material, or because there are other graduate courses which cover the areas more thoroughly. Chapters 1, 4, and 6 especially may fall into one of these categories.

Although this is a textbook, it has been designed to have reference value also. Students who are preparing for qualifying examinations and practicing organic chemists will find that Part 2 contains a survey of what is known about the mechanism and scope of about 475 reactions, arranged in an orderly manner based on reaction type and on which bonds are broken and formed. Also valuable for reference purposes are the previously mentioned lists of reactions classified by type of compound prepared (Appendix C) and of all of the *Organic Syntheses* references to each reaction.

It is a pleasure to acknowledge the assistance of a number of chemists who have been kind enough to read portions of the manuscript and to send me their comments, which were exceedingly helpful. I wish to thank Professors J. F. Bunnett, A. W. Burgstahler, D. J. Cram, P. de Mayo, E. L. Eliel, R. W. Griffin, Jr., G. S. Hammond, M. Kreevoy, S. Moon, G. A. Olah, G. C. Pimentel, W. H. Saunders, Jr., C. G. Swain, R. W. Taft, Jr., W. S. Trahanovsky, C. Walling, and R. Wistar, each of whom read one or more chapters, and Professor C. A. Bunton, who read the entire manuscript. In addition, I wish to thank many of my colleagues at Adelphi University who have rendered assistance in various ways, among them: F. Bettelheim, W. P. Gallagher, J. Landesberg, S. Moon, A. J. Sisti, and S. Windwer. Of course, the responsibility for all errors is mine alone.

Jerry March

Bibliographical Note

In this book the practices used in citing references are slightly different from those prevailing elsewhere. The reader should note:

1. For review articles, both the first and last page numbers are given, so that the reader may form an idea of the length of the article. If reference is made to only a portion of the article, these page numbers are also given.
2. Author's initials are omitted in references. They may be found, however, in the author index.
3. When a journal is available both in a foreign language and in English, the page numbers of each article are, of course, different. The language of the journal title indicates whether the page number cited is to be found in the original or in the English version.
4. Certain hardbound serial publications (see p. 946) are here cited as journals rather than as books.

Contents

Preface vii

Bibliographical Note xi

PART ONE

Introduction 1

Chapter 1 Localized Chemical Bonding 3

Chapter 2 Delocalized Chemical Bonding 28
Aromaticity, 37 *Hyperconjugation, 56*
Tautomerism, 59

Chapter 3 Bonding Weaker than Covalent 63
Hydrogen bonding, 63 *Addition compounds, 65*

Chapter 4 Stereochemistry 71
Optical isomerism and optical activity, 71
Geometrical isomerism, 94 *Conformational analysis, 101*
Strain, 116

Chapter 5 Carbonium Ions, Carbanions, Free Radicals, and Carbenes 125
Carbonium ions, 125 *Carbanions, 142* *Free radicals, 153*
Carbenes, 158

Chapter 6 Instrumental Methods for the Determination of Structure 167

Chapter 7 Mechanisms and Methods of Determining Them 199

Chapter 8 Acids and Bases 217

Chapter 9 Effects of Structure on Reactivity 231

PART TWO

Introduction 247

Chapter 10 Aliphatic Nucleophilic Substitution 251
Mechanisms, 251 *Reactivity, 281* *Reactions, 302*

Chapter 11 Aromatic Electrophilic Substitution 376
Mechanism, 376 Orientation and reactivity, 382
Reactions, 395

Chapter 12 Aliphatic Electrophilic Substitution 442
Mechanisms, 442 Reactivity, 450 Reactions, 452

Chapter 13 Aromatic Nucleophilic Substitution 488
Mechanisms, 488 Reactivity, 494 Reactions, 499

Chapter 14 Free-radical Substitution 521
Mechanisms, 521 Reactivity, 526 Reactions, 532

Chapter 15 Addition to Carbon-Carbon Multiple Bonds 562
Mechanisms, 562 Orientation and reactivity, 573
Reactions, 579

Chapter 16 Addition to Carbon-Hetero Multiple Bonds 651
Mechanism and reactivity, 651 Reactions, 653

Chapter 17 Eliminations 727
Mechanisms and orientation, 727 Reactivity, 743
Mechanisms and orientation in pyrolytic eliminations, 747
Reactions, 753

Chapter 18 Rearrangements 781
Mechanisms, 781 Reactions, 793

Chapter 19 Oxidations and Reductions 853
Mechanisms, 854 Reactions, 857

Appendix A Some Notes on the Naming of Organic Compounds 912

Appendix B The Literature of Organic Chemistry 932
Primary sources, 932 Secondary sources, 937
Literature searching, 952

Appendix C Classification of Reactions by Type of Compound Synthesized 956

Name Index 989

Subject Index 1031

Part One

This book contains 19 chapters. Chapters 10 through 19, which make up Part 2, are directly concerned with organic reactions and their mechanisms. Chapters 1 through 9 may be thought of as an introduction to Part 2. The first six chapters constitute a unit dealing with the structure of organic compounds. In this unit we shall discuss the kinds of bonding important in organic chemistry, the three-dimensional structure of organic molecules, and the structure of species in which the valence of carbon is less than four. To conclude this section, we shall treat in Chapter 6 some of the methods by means of which structure is determined. Chapters 7 to 9 are concerned with other topics which help to form a background to Part 2: acids and bases, the relationship between structure and reactivity, and a general discussion of mechanisms and of the means by which they are determined.

CHAPTER ONE

Localized Chemical Bonding

Localized chemical bonding, which is treated in this chapter, may be defined as bonding in which the electrons are shared by two and only two nuclei. In Chapter 2 we shall consider *delocalized bonding,* in which electrons are shared by more than two nuclei. But before we can intelligently discuss bonding at all, we must consider the electronic structure of atoms, in which the electrons surround only one nucleus.

Atomic Orbitals.[1] The fundamental principle upon which wave mechanics is based is that electrons behave as waves (for example, they may be diffracted) and that consequently a wave equation may be written for them, in the same sense that light waves, sound waves, etc., can be described by wave equations. The equation which serves as a mathematical model for electrons is known as the *Schrödinger equation,* and for a one-electron system is

$$\frac{\partial^2\psi}{\partial x^2} + \frac{\partial^2\psi}{\partial y^2} + \frac{\partial^2\psi}{\partial z^2} + \frac{8\pi^2 m}{h^2}(E - V)\Psi = 0 \qquad (1)$$

where m is the mass of the electron, E is its total energy, V is its potential energy, and h is Planck's constant. In physical terms, the function ψ expresses the square root of the probability of finding the electron at any position defined by the coordinates x, y, and z, where the origin is at the nucleus. For systems containing more than one electron the equation is similar, but more complicated.

The solutions to the Schrödinger equation are themselves equations. Solutions exist only for certain values of E. These are called *eigenvalues,* and the solutions are called *eigenfunctions.* This is another way of saying that the energy possessed by electrons is quantized. For the hydrogen atom, which is spherically symmetrical, the natural coordinate system is the system of spherical polar coordinates (r, θ, and ϕ), and solutions to (1) for the hydrogen atom are generally expressed in these coordinates. The spherical coordinates are related to the rectangular coordinates as follows (see Figure 1):

$$x = r \sin\theta \cos\phi \qquad (2)$$

$$y = r \sin\theta \sin\phi \qquad (3)$$

$$z = r \cos\theta \qquad (4)$$

$$r = (x^2 + y^2 + z^2)^{1/2} \qquad (5)$$

---

[1] The treatment of atomic and molecular orbitals given here is necessarily simplified. For much fuller treatments of orbital theory as applied to organic chemistry, see Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, 1961; Coulson, "Valence," 2d ed., Oxford University Press, New York, 1961; Coulson and Stewart, in Patai, "The Chemistry of Alkenes," pp. 1–147, Interscience Publishers, Inc., New York, 1964; and Higasi, Baba, and Rembaum, "Quantum Organic Chemistry," Interscience Publishers, Inc., New York, 1965.

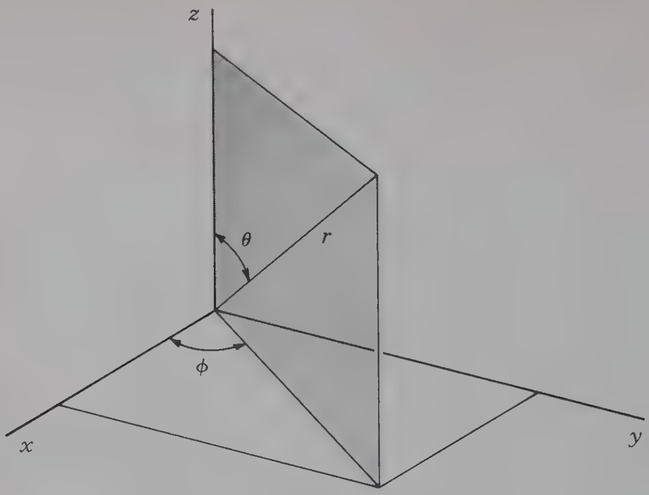


Figure 1. *The spherical coordinates.*

For a given point P, the coordinate r is the distance between the origin (O) and the point, while θ represents the angle between the line OP and the z axis, and ϕ is the angle between the xz plane and the plane containing OP and the z axis.

For the hydrogen atom, the potential energy is

$$V = -\frac{Ze^2}{r} \tag{6}$$

where r is the distance between the nucleus and the electron, e the charge on the electron, and Z the nuclear charge (in this case, 1). The solution of the Schrödinger equation which corresponds to the lowest possible energy for the electron is

$$\psi = \frac{1}{\sqrt{\pi}}\left(\frac{Z}{a_0}\right)^{3/2} e^{-Zr/a_0} \tag{7}$$

where

$$a_0 = \frac{h^2}{4\pi^2 me^2} \tag{8}$$

The energy corresponding to this solution is

$$E = \frac{-2\pi m Z^2 e^4}{h^2} \tag{9}$$

which turns out to be −13.60 electron volts. The distance a_0, which is equal to 0.529 Å, is called the *Bohr radius.*

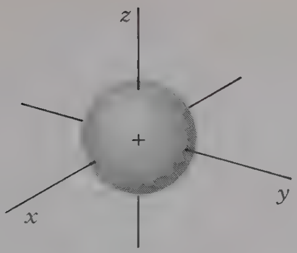


Figure 2. *The wave function for the lowest energy level (ground state) of the hydrogen atom.*

Three of the higher solutions are

$$\psi = \frac{1}{\sqrt{32\pi}}\left(\frac{Z}{a_0}\right)^{5/2} re^{-Zr/2a_0} \cos\theta \tag{10}$$

$$\psi = \frac{1}{\sqrt{64\pi}}\left(\frac{Z}{a_0}\right)^{5/2} re^{-Zr/2a_0} \sin\theta\cos\phi \tag{11}$$

$$\psi = \frac{1}{\sqrt{64\pi}}\left(\frac{Z}{a_0}\right)^{5/2} re^{-Zr/2a_0} \sin\theta\sin\phi \tag{12}$$

Since the energies corresponding to these three eigenfunctions are equal, the energy levels are said to be degenerate. There are an infinite number of other solutions, each with its corresponding energy, but there are no solutions with an energy between those of any two successive solutions.

Since these eigenfunctions are equations, we may graph them. The graphs are three-dimensional pictures of the density of the electron. The graph corresponding to Eq. (7) shows that the electron density is distributed symmetrically about the nucleus. The density increases along a line beginning at the nucleus and proceeding in any direction until a maximum is reached, after which it rapidly drops off. This maximum is at $r = 0.529$ Å; that is, it is at the Bohr radius. Although in theory there is still some density at an infinite distance from the nucleus, it is possible to draw a sphere with a radius of about four or five times that of the Bohr radius and enclose nearly all the electron density in it. Such a sphere is shown in Figure 2.

A wave function like that depicted in Figure 2 is called an *orbital*, or an electron cloud. Some are spherical, like that in Figure 2. These are called *s* orbitals. The orbital corresponding to Eq. (10), shown in Figure 3, is called a *p* orbital. Unlike *s* orbitals, *p* orbitals are not spherically symmetrical but are directed along one of the axes. Note that there is no probability of finding the electron at any point on the *xy* plane. Any such region in space is called a *node*. In Figure 3 one lobe of the orbital is labeled + and the other −. These signs do not refer to positive or negative *charges*, since both lobes of an electron cloud must be negatively charged. They are the signs of the function ψ. When two parts of any orbital are separated by a node, then ψ always has opposite signs on the two sides of the node.

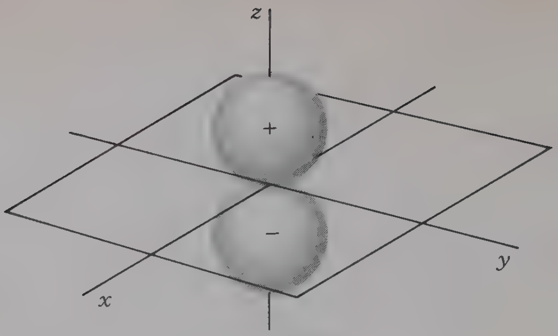
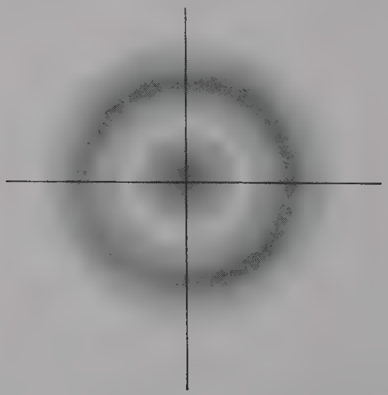


Figure 3. *The orbital corresponding to Eq. (10).*

The orbitals corresponding to Eqs. (11) and (12) have the same shape as the one in Figure 3, but they are directed along the other axes. The three *p* orbitals are often called p_x, p_y, and p_z, to distinguish among them. There are also orbitals of higher energy, called *d* and *f* orbitals, but we shall not consider their shapes here, since they are less important to organic chemists than the *s* and *p* orbitals.

The orbital shown in Figure 2 corresponds to the lowest possible energy for the electron of the hydrogen atom. It is called the 1*s* orbital. If we examine the eigenfunctions corresponding to the next energy value, we find four degenerate orbitals. One of these, called the 2*s* orbital, is spherical and contains a node (Figure 4). The others are the three *p* orbitals mentioned before, which are called 2*p* orbitals. Orbitals of higher energy are 3*s*, 3*p*, 3*d*, 4*s*, etc. In any given hydrogen atom, the electron at any instant is in only one of these orbitals. The others exist only as potential states. However it is possible (and often happens) that an electron may pass from one orbital to

Figure 4. *Cross section of a 2s orbital.*



another. When this occurs, the orbital previously occupied becomes a potential state, and the new one is occupied. In order for an electron to go from a lower-energy orbital to a higher one, it must get energy from somewhere; and when it goes from a higher to a lower state, it must give up the necessary energy. Not all transitions are allowed; selection rules determine the ones which can occur. When the electron is in the 1*s* orbital, the hydrogen atom is said to be in the *ground state.* All levels above the ground state are called *excited states.*

Unfortunately, the Schrödinger equation can be solved exactly only for one-electron atomic systems, such as the hydrogen atom or He^+. For all systems more complicated than this, approximations are required. For a number of simple cases, such as the hydrogen molecule and the helium atom, these approximate solutions are so accurate that for practical purposes they are as good as exact solutions.[2] Even for atoms much larger than helium, a good qualitative picture is at hand. By the use of the following principles, electronic structures may be determined for atoms up to about calcium:

1. In any atom the orbitals available for electron occupancy are similar in shape to those of the hydrogen atom, though the energies are different. The designations 1*s*, 2*s*, 2*p*, etc., are the same.
2. In the ground state of any atom the electrons occupy the lowest possible energy levels. If even one electron is in an orbital of energy higher than a vacant orbital, the atom is in an excited state.
3. No more than two electrons may be present in an orbital, and these must have opposite spins.[3] This is the *Pauli exclusion principle.*
4. When a number of degenerate orbitals are available, and there are not enough electrons to fill all of them, then all the orbitals will be half-filled before any of them are filled. This is called *Hund's rule.* For example, the nitrogen atom has seven electrons. Four of these are accommodated in the two orbitals of lowest energy: the 1*s* and 2*s* orbitals. Above these are the three *p* orbitals, which can hold a maximum of six electrons. Hund's rule tells us that each of the three remaining electrons will go into a different 2*p* orbital; i.e., the configuration of the ground state of the nitrogen atom is $1s^2 2s^2 2p_x{}^1 2p_y{}^1 2p_z{}^1$ and not $1s^2 2s^2 2p_x{}^2 2p_y{}^1$. Hund's rule is valid because a situation in which two electrons have parallel spins is of lower energy than that in which the spins are opposite, owing to the greater mutual repulsion of electrons with opposite spins. In the case of a $2p_x{}^2 2p_y{}^1$ configuration, two of the electrons must have opposite spins (or they could not be in the same orbital), while for $2p_x{}^1 2p_y{}^1 2p_z{}^1$ all the spins may be and generally are parallel.

For atoms higher than hydrogen, the energy of the orbitals is in the order $1s < 2s < 2p < 3s < 3p < 4s$. From this, and the above rules, the electronic structures for the ground states of the first 20 atoms are

---

[2] See, for example, Roothaan and Weiss, *Rev. Mod. Phys.* **32,** 194 (1960); Kolos and Roothan, *Rev. Mod. Phys.* **32,** 219 (1960).

[3] In this book we shall not define electron spin but merely state that it is a property of an electron for which two and only two possible states exist.

H	$1s^1$	**Na**	**Ne** core $3s^1$
He	$1s^2$	**Mg**	**Ne** core $3s^2$
Li	$1s^22s^1$	**Al**	**Ne** core $3s^23p_x{}^1$
Be	$1s^22s^2$	**Si**	**Ne** core $3s^23p_x{}^13p_y{}^1$
B	$1s^22s^22p_x{}^1$	**P**	**Ne** core $3s^23p_x{}^13p_y{}^13p_z{}^1$
C	$1s^22s^22p_x{}^12p_y{}^1$	**S**	**Ne** core $3s^23p_x{}^23p_y{}^13p_z{}^1$
N	$1s^22s^22p_x{}^12p_y{}^12p_z{}^1$	**Cl**	**Ne** core $3s^23p_x{}^23p_y{}^23p_z{}^1$
O	$1s^22s^22p_x{}^22p_y{}^12p_z{}^1$	**Ar**	**Ne** core $3s^23p_x{}^23p_y{}^23p_z{}^2$
F	$1s^22s^22p_x{}^22p_y{}^22p_z{}^1$	**K**	**Ar** core $4s^1$
Ne	$1s^22s^22p_x{}^22p_y{}^22p_z{}^2$	**Ca**	**Ar** core $4s^2$

It is the custom to designate the first occupied orbital of a set of p orbitals as the p_x orbital. Of course, this is purely arbitrary, since the three p orbitals differ only in direction. For example, it would be just as correct to show the electronic structure of boron as $1s^22s^22p_y{}^1$ or $1s^22s^22p_z{}^1$.

Covalent Bonding. If the Schrödinger equation could be exactly solved for molecules, then we would have a complete picture which would show for each electron precisely the shape of the orbitals available to it (especially for the important ground state), and the energy for each orbital. Since exact solutions are not available, drastic approximations must be made. There are two chief methods of approximation, called the *molecular-orbital* method and the *valence-bond* method.

In the molecular-orbital method, bonding is considered to arise from the overlap of two atomic orbitals. The overlap of two orbitals, each containing one electron, gives rise to two new orbitals, which are clouds surrounding the nuclei of the two atoms. These are called *molecular orbitals.* One of them, called a *bonding orbital,* has a lower energy than the original atomic orbitals (otherwise a bond would not form), and the other, called an *antibonding orbital,* has a higher energy. Whereas the two original atomic orbitals each held one electron, both of these electrons may now go into the new molecular *bonding* orbital, since any orbital can hold two electrons. The antibonding orbital remains empty in the ground state. The greater the overlap, the stronger the bond, although total overlap is prevented by repulsion between the nuclei. Figure 5 shows the bonding and antibonding orbitals which arise by overlap of two $1s$ electrons. Molecular orbitals formed by overlap of two atomic orbitals, when the centers of electron density are on the axis common to the two nuclei, are called σ orbitals. Corresponding antibonding orbitals are designated σ^*. This type of orbital may be formed by overlap of any of the kinds of atomic orbitals mentioned earlier (s, p, d, or f) whether they are the same or different. Any σ orbital may be approximately represented as ellipsoidal in shape.

In molecular-orbital calculations, a wave function is formulated which is a linear combination of the atomic orbitals which have overlapped (this method is often called the *linear combination of atomic orbitals,* or LCAO):

$$\Psi = c_A\psi_A + c_B\psi_B \tag{13}$$

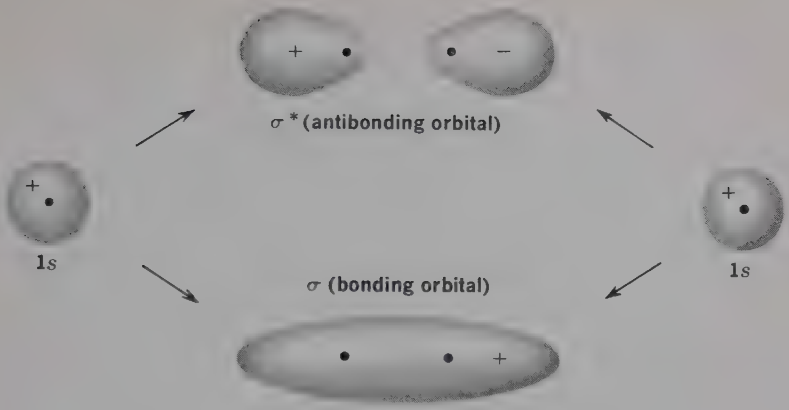


Figure 5. *Overlap of two 1s orbitals gives rise to a σ and a σ* orbital.*

The functions ψ_A and ψ_B are the functions for the atomic orbitals of atoms A and B, respectively, and c_A and c_B represent weighting factors.

In the valence-bond method, a wave equation is written for each of various possible electronic structures which a molecule may have (each of these is called a *canonical form*), and the total Ψ is obtained by summation of as many of these as seem plausible, each with its weighting factor:

$$\Psi = c_A\psi_A + c_B\psi_B + \cdots \tag{14}$$

This resembles Eq. (13), but here each ψ represents a wave equation for an imaginary canonical form, and each c is the amount contributed to the total picture by that form. For example, a wave function may be written for each of the following canonical forms of the hydrogen molecule:[4]

$$\dot{\mathrm{H}}\,\dot{\mathrm{H}} \qquad \bar{\mathrm{H}}\,\mathrm{H} \qquad \mathrm{H}\,\bar{\mathrm{H}}$$

Values for c in each method are obtained by solving the equation for various values of each c and choosing the solution of lowest energy. In practice, both methods give similar solutions for molecules which contain only localized electrons, and these are in agreement with the Lewis structures long familiar to the organic chemist. Delocalized systems are considered in Chapter 2.

Multiple Valence. A univalent atom has only one orbital available for bonding. But atoms with a valence of two or more must form bonds by using at least two orbitals. From our previous discussion of atomic orbitals, we have seen that the oxygen atom has two half-filled orbitals, thus giving it a valence of two. It forms single bonds by overlap of these with the orbitals of two

---

[4] In this book a pair of electrons, whether in a bond or unshared, is represented by a straight line.

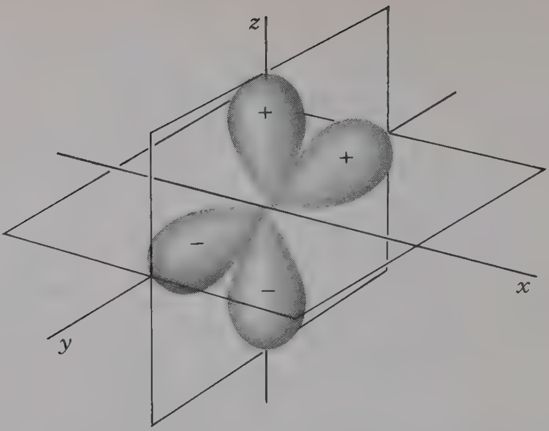


Figure 6. *The p orbitals of oxygen which are available for bonding.*

other atoms. According to the principle of maximum overlap, the other two nuclei should form an angle of 90° with the oxygen nucleus, since the two available orbitals on oxygen are *p* orbitals, which are perpendicular (Figure 6). Similarly, we should expect that nitrogen, which has three mutually perpendicular *p* orbitals, would have bond angles of 90° when it forms three single bonds. However, these are not the observed bond angles. The bond angles are,[5] in water, 104°27′, and in ammonia, 106°46′. For alcohols and ethers the angles are even larger (see p. 24). A discussion of this will be deferred to the next section, but it is important to note that covalent compounds do have definite bond angles. Although the atoms are continuously vibrating (see Chapter 6), the mean position is the same for each molecule of a given compound.

Hybridization. Consider the case of mercury. Its electronic structure is

$$\textbf{Xe}\text{ core } 4f^{14}5d^{10}6s^2$$

Although it has no half-filled orbitals, it has a valence of two and forms two covalent bonds. We may explain this by imagining that one of the 6*s* electrons is promoted to a vacant 6*p* orbital to give the configuration

$$\textbf{Xe}\text{ core } 4f^{14}5d^{10}6s^1 6p^1$$

In this state the atom has two half-filled orbitals, but they are not equivalent. If bonding were to occur by overlap of these orbitals with the orbitals of external atoms, the two bonds would not be equivalent, and the bond formed from the 6*p* orbital would be more stable than the one formed from the 6*s* orbital, since a larger amount of overlap is possible with the former.

---

[5] Bent, *Chem. Rev.* **61**, 275–311 (1961), p. 277.

A more stable situation is achieved when, in the course of bond formation, the 6*s* and 6*p* orbitals combine to form two new orbitals which *are* equivalent; these are shown in Figure 7.

Since these new orbitals are a mixture of the two original orbitals, they are called *hybrid orbitals.* Each is called an *sp* orbital, since a merger of an *s* and a *p* orbital was required to form it. The *sp* orbitals are atomic orbitals, although they can arise only in the bonding process and do not represent a possible structure for the free atom. The molecular orbital which arises from overlap of an *sp* orbital and an atomic orbital from another atom is called a σ orbital, since it fits our previous definition of a σ orbital (p. 8).

In general, equivalent orbitals lie as far away from each other as possible, and so the two *sp* orbitals form an angle of 180°. This means that $HgCl_2$, for example, should be a linear molecule (in contrast to H_2O), and it is. This kind of hybridization is called *digonal* hybridization. An *sp* hybrid orbital forms a stronger covalent bond than either an *s* or a *p* orbital because it extends out in space in the direction of the other atom's orbital farther than the *s* or the *p* and so permits greater overlap. Although it would require energy to promote a 6*s* electron to the 6*p* state, the extra bond energy more than makes up the difference.

Many other kinds of hybridization are possible, of which we shall discuss two. Consider boron, which has the electronic configuration

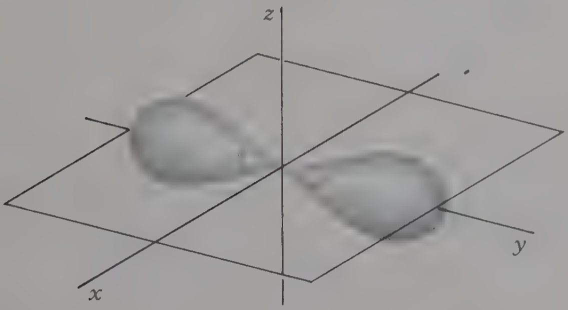
$$1s^2 2s^2 2p^1$$

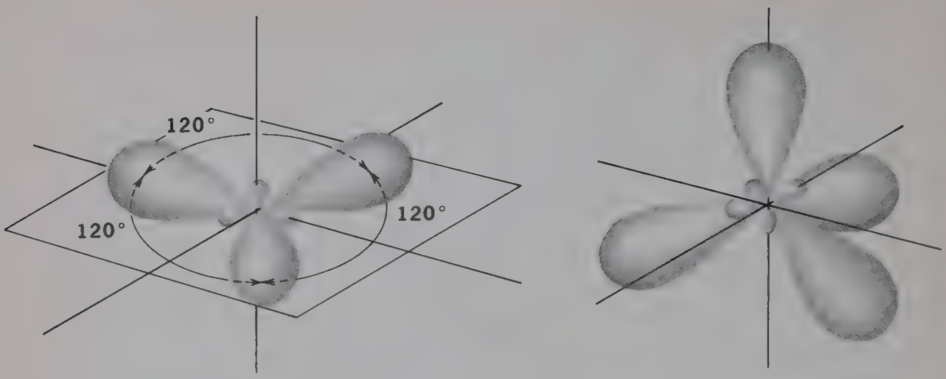
yet has a valence of three. Once again we may imagine promotion and hybridization:

$$1s^2 2s^2 2p^1 \longrightarrow 1s^2 2s^1 2p_x{}^1 2p_y{}^1 \longrightarrow 1s^2(sp^2)^3$$

In this case there are three equivalent hybrid orbitals, each called sp^2 (*trigonal* hybridization). This method of designating hybrid orbitals is perhaps unfortunate since nonhybrid orbitals are designated by single letters, but it must be kept in mind that *each* of the three orbitals is called sp^2. These

Figure 7. *The two sp orbitals formed by mercury.*





sp^2 **orbitals**

sp^3 **orbitals**

Figure 8. *The three sp*^{2} *and the four sp*^{3} *orbitals.*

orbitals are shown in Figure 8. The three axes are all in one plane and point to the corners of an equilateral triangle. This is in accord with the known structure of BF_3, a planar molecule with angles of 120°.

The case of carbon (in forming four single bonds) may be represented as follows:

$$1s^2 2s^2 2p_x^1 2p_y^1 \longrightarrow 1s^2 2s^1 2p_x^1 2p_y^1 2p_z^1 \longrightarrow 1s^2 (sp^3)^4$$

Here there are four equivalent orbitals, each called sp^3, which point to the corners of a regular tetrahedron (Figure 8). The bond angles of methane would thus be expected to be 109°28′, which is the angle for a regular tetrahedron.

The larger-than-expected bond angles of water and ammonia (p. 10) have been ascribed[5] to sp^3 hybridization. According to this view, the unshared pair in ammonia is not in a $2s^2$ orbital (where it would have to be spherically symmetrical), but in the fourth sp^3 orbital, though not bonded. Consequently, the bond angles should be 109°28′. The fact that the angles are in fact smaller than this has been explained in several ways. It has been held that an unshared pair is actually larger than a pair in a bond, since there is no second nucleus to draw away some of the electron density, and that the bonds are thus crowded together.[6] Another explanation is based on the fact that hybridization need not involve an integral number of atomic orbitals, that is, *s* and *p* orbitals may mix in fractional proportions as well as in strict 1:1, 1:2, and 1:3 ratios. According to this explanation, water and ammonia do not have complete sp^3 hybridization, but additional *p* character is involved, which reduces the angle somewhat. The matter is not yet settled.

It is possible to explain the known shapes of inorganic molecules without using the concept of hybridization at all,[7] but we shall use it in this book, since much of the organic chemical literature is written in these terms.

---

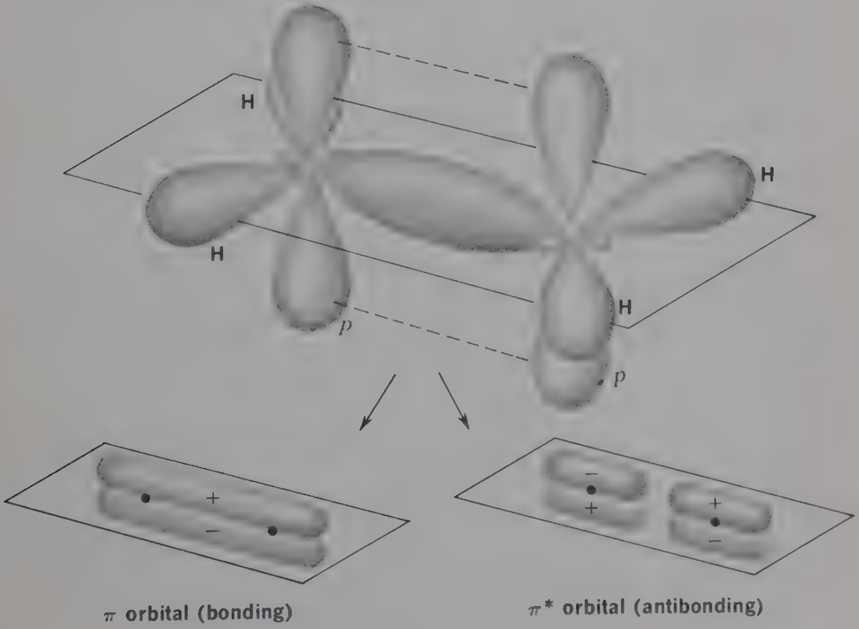
[6] For evidence against this view, see Allinger, Carpenter, and Karkowski, *Tetrahedron Letters* **1964**, 3345; and Eliel and Knoeber, *J. Am. Chem. Soc.* **88,** 5347 (1966).

Multiple Bonds. If we consider the ethylene molecule in terms of the molecular-orbital concepts so far discussed, we have each carbon using sp^2 orbitals to form bonds with the three atoms to which it is connected. These sp^2 orbitals arise from hybridization of the $2s^1$, $2p_x^1$, and $2p_y^1$ electrons of the promoted state shown on p. 12. We may consider that any carbon atom which is bonded to only three different atoms uses sp^2 orbitals for this bonding. Each carbon of ethylene is thus bonded by three σ bonds: one to each hydrogen, and one to the other carbon. Each carbon therefore has another electron in the $2p_z$ orbital which, by the principle of maximum repulsion, is perpendicular to the plane of the sp^2 orbitals. The two $2p_z$ orbitals can overlap to generate two new orbitals, a bonding and an antibonding orbital (Figure 9). Of course, both of the electrons go into the bonding orbital, and the antibonding orbital remains vacant, in the ground state. Molecular orbitals which are formed by overlap of atomic orbitals whose axes are parallel are called π orbitals if they are bonding and π^* if they are antibonding.

---

[7] See Gillespie, *J. Chem. Educ.* **40**, 295 (1963).

Figure 9. *Overlapping p orbitals form a π and a π^* orbital. The σ orbitals are shown in the upper figure. They are still there in the diagrams below, but have been removed from the picture for clarity.*



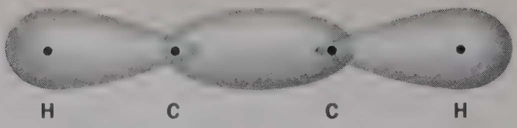
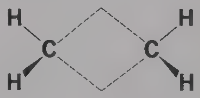


Figure 10. *The σ electrons of acetylene.*

In this picture of ethylene, the two orbitals which make up the double bond are not equivalent. The σ orbital is ellipsoidal, and is symmetrical about the C—C axis. The π orbital is in the shape of two ellipsoids, one above the plane and one below. The plane itself represents a node for the π orbital. In order for the *p* orbitals to maintain maximum overlap, they must be parallel. This means that free rotation is not possible about the double bond, since the two *p* orbitals would have to reduce their overlap to allow one H—C—H plane to rotate with respect to the other. The six atoms of a double bond are therefore in a plane with angles which should be about 120°.

The lack of free rotation about double bonds may also be explained by the "bent-bond" picture.[8] In this picture, the two bonds in the double bond of the ethylene molecule are equivalent. The centers of electron density are pointed *away* from the C—C axis:



That is, all four of the bonds of each carbon point to the corners of a tetrahedron. This is essentially the old picture of formation of a double bond by the joining together of two tetrahedra along one edge. Although there are some reasons to support this picture,[9] rather than the σ-π concept, in this book we shall use the latter, because most of the recent literature is written in these terms. Similar pictures of both kinds may be drawn for double bonds between carbon and oxygen or nitrogen.

In triple-bond compounds, carbon is connected to only two other atoms, and hence uses *sp* hybridization, which means that the four atoms involved are in a straight line (Figure 10). Each carbon has two *p* orbitals remaining, with one electron in each. These orbitals are perpendicular to each other, and to the C—C axis. They overlap in the manner shown in Figure 11 to form two π orbitals. A triple bond is thus composed of one σ and two

---

[8] Pauling, in "Theoretical Organic Chemistry, The Kekulé Symposium," pp. 2–5, Butterworth Scientific Publications, London, 1959. Bent bonds are also called "banana bonds."

[9] For example, the σ-π picture predicts an H—C—C angle of 120°, while this angle in the bent-bond picture would be 125°16′. Although the H—C—C angle in ethylene is about 121 to 122°, the corresponding angle is larger for other olefins: 124.8° for propylene, 124° for isobutylene, etc. (see Ref. 8). Also, charge-density calculations show that in ethylene the electrons associated with the C—C bond tend to accumulate above and below the molecular plane [Roux, Cornille, and Burnelle, *J. Chem. Phys.* **37**, 933 (1962)].

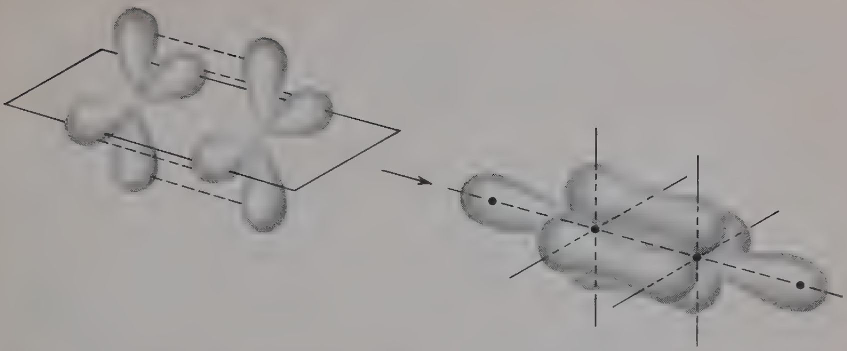


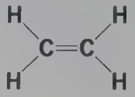
Figure 11. *Overlap of p orbitals in a triple bond. For clarity, the σ orbitals have been removed from the drawing on the left, though they are shown on the right.*

π orbitals. (In the bent-bond picture, a triple bond is made up of two tetrahedra with a common face.) Triple bonds between carbon and nitrogen may be represented in a similar manner.

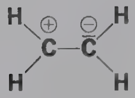
Electronic Structures of Molecules. For each molecule, ion, or free radical which has only localized electrons, it is possible to draw an electronic formula, called a *Lewis structure,* which shows the location of these electrons. In practice only the valence electrons are shown. These may be found in covalent bonds connecting two atoms, or they may be unshared. It is important that the student be able to draw these structures correctly, since the position of electrons changes in the course of a reaction, and it is necessary to know which orbitals the electrons are in initially before one can follow where they are going. To this end, the following rules operate:

1. The total number of valence electrons in the molecule (or ion or free radical) must be the sum of all outer-shell electrons "contributed" to the molecule by each atom, plus the negative charge or minus the positive charge, for the case of ions. Thus, for H_2SO_4, there are 2 (one for each hydrogen) + 6 (for the sulfur) + 24 (6 for each oxygen) = 32; while for $SO_4^=$, the number is also 32, since each atom "contributes" 6, plus 2 for the negative charge.
2. Once the number of valence electrons has been ascertained, it is necessary to determine which of them are found in covalent bonds and which are unshared. Unshared electrons (either a single electron or a pair) form part of the outer shell of just one atom, but electrons in a covalent bond are part of the outer shell of both atoms of the bond. *First-row atoms* (B, C, N, O, F) *can have a maximum of eight valence electrons,* and usually have this number, although some cases are known where a first-row atom has only six or seven. Where there is a choice between a structure which has six or seven electrons around a first-row atom and one in which all such atoms have an octet, it is the latter which generally has the lower energy and which conse-

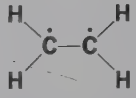
quently exists. For example, ethylene is



and not



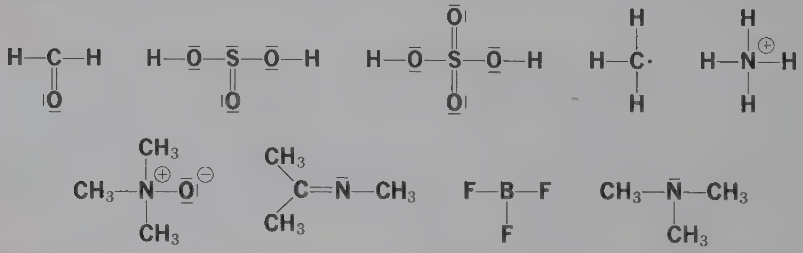
or



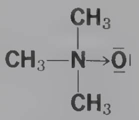
There are a few exceptions. In the case of the molecule O_2, the structure $|\dot{\underline{O}}-\dot{\underline{O}}|$ has a lower energy than $|\underline{O}=\underline{O}|$. Although first-row atoms are limited to 8 valence electrons, this is not so for second-row atoms, which can accommodate 10 or even 12.[10]

3. It is customary to show the formal charge on each atom. For this purpose an atom is considered to "own" all unshared electrons, but only *one-half of the electrons in covalent bonds.* The sum of electrons which thus "belong" to an atom is compared to the number "contributed" by the atom. An excess belonging to the atom results in a negative charge, and a deficiency results in a positive charge. The total of the formal charges on all atoms equals the charge on the whole molecule or ion. It should be noted that the counting procedure is not the same for determining formal charge as it is for determining the number of valence electrons. For both purposes an atom "owns" all unshared electrons, but for outer-shell purposes it "owns" both of the electrons of the covalent bond, while for formal-charge purposes, it "owns" only one-half of these electrons.

Examples of electronic structures are (as mentioned in footnote 4, in this book an electron pair, whether unshared or in a bond, is represented by a straight line):



A coordinate-covalent bond, represented by an arrow, is one in which both electrons come from the same atom; that is, the bond may be regarded as being formed by overlap of an orbital containing two electrons with an empty one. Thus trimethylamine oxide would be represented



$$CH_3-N(CH_3)_2\rightarrow\bar{O}|$$

---

[10] For a review concerning sulfur compounds with a valence shell larger than eight, see Cilento, *Chem. Rev.* **60**, 147–167 (1960).

For a coordinate-covalent bond the rule concerning formal charge is amended, so that both electrons count for the donor and neither for the recipient. Thus, as written here, the nitrogen and oxygen atoms of trimethylamine oxide bear no formal charges. However, it is apparent that the electronic picture is exactly the same as the picture of trimethylamine oxide given just above, and we have our choice of drawing an arrowhead or a charge separation. Some compounds, for example, amine oxides, must be drawn one way or the other. It seems simpler to use charge separation, since this spares us from having to consider as a "different" method of bonding, a way that is really the same as ordinary covalent bonding once the bond has formed.[11]

Electronegativity.[12] The electron cloud which bonds two atoms is not symmetrical (with respect to the plane which is the perpendicular bisector of the bond) except when the two atoms are the same and have the same substituents. The cloud is necessarily distorted toward one side of the bond or the other, depending on which atom (nucleus plus electrons) maintains the greater attraction for the cloud. This attraction is called *electronegativity* and is greatest for atoms in the upper right corner of the periodic table, and lowest for atoms in the lower left corner. Thus a bond between fluorine and chlorine will be distorted so that there is a higher probability of finding the electrons near the fluorine than near the chlorine. This gives the fluorine a partial negative charge and the chlorine a partial positive charge.

A number of attempts have been made to set up quantitative tables of electronegativity, which would indicate the direction and extent of electron-cloud distortion for a bond between any pair of atoms. The most popular of these scales, devised by Pauling, is based on bond energies (see p. 24) of diatomic molecules. The reasoning here is: if in a molecule A—B the electron distribution were symmetrical, then the bond energy would be the mean of the energies of A—A and B—B, since in these cases the cloud must be undistorted. If the actual bond energy of A—B is higher than this (and it usually is), then this is the result of the partial charges, since the charges attract each other, and make a stronger bond, which requires more energy to break. It is necessary to assign a value to one element arbitrarily (F = 4.0 is the one used); then the electronegativity of another is obtained from the difference between the actual energy of A—B and the mean of A—A and B—B (this difference is called Δ) by the formula:

$$x_A - x_B = \sqrt{\frac{\Delta}{23.06}} \tag{15}$$

---

[11] It has recently been suggested that the valence octet around atoms may be better understood as being made up of two quartets rather than four pairs. For this argument see Linnett, "The Electronic Structure of Molecules," John Wiley & Sons, Inc., New York, 1964, and the following papers: Hirst and Linnett, *J. Chem. Soc.* **1962,** 1035; Hopton and Linnett, *J. Chem. Soc.* **1962,** 1553; Linnett, *J. Am. Chem. Soc.* **83,** 2643 (1961); Empedocles and Linnett, *Proc. Chem. Soc.* **1963,** 303; Hirst, Hopton, and Linnett, *Tetrahedron* **19,** Suppl. 2, 15 (1963); Linnett and Rosenberg, *Tetrahedron* **20,** 53 (1964).

[12] For reviews of this topic, see Syrkin, *Russ. Chem. Rev.* **31,** 197–206 (1962); Pritchard and Skinner, *Chem. Rev.* **55,** 745–786 (1955); and Pauling, "The Nature of the Chemical Bond," 3d ed., Cornell University Press, Ithaca, N.Y., 1960.

TABLE 1. Electronegativities of some atoms[13]

F	4.0	P	2.1
O	3.5	H	2.1
N	3.0	B	2.0
Cl	3.0	Si	1.8
Br	2.8	Mg	1.2
S	2.5	Na	0.9
C	2.5	Cs	0.7
I	2.5		

where x_A and x_B are the electronegativities of the known and unknown atoms, and 23.06 is an arbitrary constant. Part of the scale derived from this treatment is shown in Table 1.[13]

Other treatments have led to scales which are based on different principles, for example, the sum of the ionization potential and the electron affinity,[14] or on the same principle with corrections.[15] In some of these treatments electronegativities may be calculated for different valence states, for different hybridizations (for example, *sp* carbon atoms are more electronegative than sp^2, which are still more electronegative than sp^3),[16] and even differently for primary, secondary, and tertiary carbon atoms. Also, electronegativities may be calculated for groups, rather than atoms (Table 2).[17]

When the difference in electronegativities is great, the orbital may be so far over to one side that it barely covers the other nucleus. This is an *ionic bond,* which is seen to arise naturally out of the previous discussion, leaving us with basically only one type of bond in organic molecules. Most bonds may be considered as intermediate between ionic and covalent. We may speak of percent ionic character of a bond, which indicates the extent of electron-cloud distortion. There is a continuous graduation from ionic to covalent bonds.

The *dipole moment* is a property of the molecule which results from charge separations like those discussed above. However, it is not possible to measure the dipole moment of an individual bond within a molecule; we can measure only the total moment of the molecule, which is the vectorial sum

TABLE 2. Some group electronegativities[17]

CH_3	2.30	$CHCl_2$	2.63
CH_2Cl	2.47	CCl_3	2.79
CI_3	2.50	CF_3	3.29
CBr_3	2.57		

---

[13] Taken from Pauling, Ref. 12, p. 93.

[14] Hinze and Jaffé, *J. Am. Chem. Soc.* **84**, 540 (1962); Iczkowski and Margrave, *J. Am. Chem. Soc.* **83**, 3547 (1961).

[15] Brown, *J. Am. Chem. Soc.* **83**, 36 (1961).

[16] Walsh, *Discussions Faraday Soc.* **2**, 18 (1947).

[17] Hinze, Whitehead, and Jaffé, *J. Am. Chem. Soc.* **85**, 148 (1963).

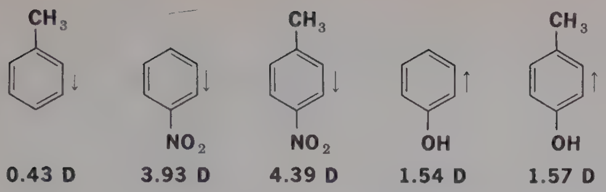


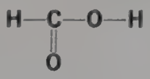
Figure 12. *Some dipole moments, in Debye units, measured in benzene. The arrow points to the negative part of the molecule.*[18]

of the individual bond moments.[19] These individual moments are roughly the same from molecule to molecule, but this constancy is by no means universal. Thus, from the dipole moments of toluene and nitrobenzene (Figure 12) we should expect the moment of *p*-nitrotoluene to be about 4.36 D. The actual value 4.39 D is quite reasonable. However, the moment of *p*-cresol (1.57 D) is quite far from the predicted value of 1.11 D.

Because of the small difference between the electronegativities of carbon and hydrogen, alkanes have very small dipole moments, so small that they are difficult to measure. For example, the dipole moment of isobutane is 0.132 D[20] and that of propane is 0.083 D.[21] Of course, methane and ethane have no dipole moments. Few organic molecules have dipole moments greater than 7 D.

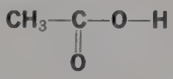
Inductive Effects. The charge separation in one bond may induce a separation in an adjacent bond, or even farther along a chain. This permanent dipole induced in one bond by another is called the *inductive effect.* Inductive effects may also be transmitted in ways other than directly along a chain, for example, through space and through solvent molecules. Such effects are often called *field effects.*[22]

A comparison of the acidities of formic and acetic acids furnishes an illustration of the operation of inductive effects.



$$H-\underset{\underset{O}{\|}}{C}-O-H$$

p*K* = 3.77



$$CH_3-\underset{\underset{O}{\|}}{C}-O-H$$

p*K* = 4.76

---

[18] The values for toluene, nitrobenzene, and *p*-nitrotoluene are from McClellan, Ref. 19. The values for phenol and *p*-cresol were determined by Goode and Ibbitson, *J. Chem. Soc.* **1960,** 4265.

[19] For methods of determining dipole moments and a discussion of their applications, see Sutton, in Braude and Nachod, "Determination of Organic Structures by Physical Methods," vol. 1, pp. 373–425, Academic Press Inc., New York, 1955. For tables of dipole moments, see McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman and Company, San Francisco, 1963; and Landolt-Börnstein, "Zahlenwerte und Funktionen," I Band, 3 Teil, pp. 388–508, Springer-Verlag OHG, Berlin, 1951.

[20] Maryott and Birnbaum, *J. Chem. Phys.* **24,** 1022 (1956); Lide and Mann, *J. Chem. Phys.* **29,** 914 (1958).

[21] Lide, *J. Chem. Phys.* **33,** 1514 (1960).

[22] It has been maintained that transmission along a chain is unimportant, and that "the inductive effect is in reality a field effect." Dewar and Grisdale, *J. Am. Chem. Soc.* **84,** 3548 (1962); Dewar and Marchand, *J. Am. Chem. Soc.* **88,** 354 (1966).

TABLE 3. p*K* values for some acids[23]

Acid	p*K*	*Acid*	p*K*
$HCOOH$	3.77	$ClCH_2CH_2COOH$	4.08
CH_3COOH	4.76	$Cl_2CHCOOH$	1.29
CH_3CH_2COOH	4.88	Cl_3CCOOH	0.65
$CH_3(CH_2)_nCOOH$[23a]	4.82–4.95		
$(CH_3)_2CHCOOH$	4.86	O_2NCH_2COOH	1.68
$(CH_3)_3CCOOH$	5.05	$(CH_3)_3\overset{\oplus}{N}CH_2COOH$	1.83
		$HOOCCH_2COOH$	2.83
FCH_2COOH	2.66	$PhCH_2COOH$	4.31
$ClCH_2COOH$	2.86	$\overset{\ominus}{O}OCCH_2COOH$	5.69
$BrCH_2COOH$	2.86	$\overset{\ominus}{O}_3SCH_2COOH$	4.05
ICH_2COOH	3.12	$HOCH_2COOH$	3.83
		$H_2C{=}CHCH_2COOH$	4.35
$ClCH_2CH_2CH_2COOH$	4.52		
$CH_3CHClCH_2COOH$	4.06		
$CH_3CH_2CHClCOOH$	2.80		

For this purpose acidity may be defined as ability to donate a proton (see Chapter 8), and acetic acid is about 10 times weaker than formic, though the only structural difference is the replacement of hydrogen by methyl. Compared to hydrogen, a methyl group is electron-releasing, when connected to an unsaturated carbon atom, as in this case.[24] This means that the electron cloud between CH_3 and C in acetic acid lies closer to the C=O carbon than does the cloud between H and C in formic acid. It is often said that, compared to hydrogen, methyl is an electron-donating group; however, there is no actual donation or release of electrons, although these terms are convenient to use. There is merely a difference in position of the electrons due to the difference in electronegativity between hydrogen and methyl. This difference induces a difference in the position of the electron cloud in the adjacent bond: the C—O electrons lie closer to the oxygen in acetic acid than in formic acid. This difference in turn affects the O—H bond, and this electron cloud lies closer to the hydrogen in acetic acid than in formic acid. A greater electron density around the hydrogen causes it to be lost less easily from acetic acid than from formic.

The acidities of carboxylic acids, which can be measured accurately, provide an excellent way of examining inductive effects of groups, though inductive effects are not the sole cause of the acidity differences shown in Table 3 (see

---

[23] These values are taken from Brown, McDaniel, and Häflinger, in Braude and Nachod, "Determination of Organic Structures by Physical Methods," vol. 1, pp. 575–582, Academic Press Inc., New York, 1955.

[23a] $n = 2$ to 7.

[24] There is evidence that the methyl group is not electron-releasing when connected to *saturated* carbon; it either has no effect, or is slightly electron-withdrawing. Kwart and Takeshita, *J. Am. Chem. Soc.* **86**, 1161 (1964); Fort and Schleyer, *J. Am. Chem. Soc.* **86**, 4194 (1964); Holtz and Stock, *J. Am. Chem. Soc.* **87**, 2404 (1965); Laurie and Muenter, *J. Am. Chem. Soc.* **88**, 2883 (1966).

TABLE 4. Inductive effects of various groups relative to hydrogen The groups are listed approximately in order of decreasing strength, for both $-I$ and $+I$ groups

$+I$	$-I$		
O^-	NR_3^+	COOH	OR
COO^-	SR_2^+	F	COR
CR_3	NH_3^+	Cl	SH
CHR_2	NO_2	Br	SR
CH_2R	SO_2R	I	OH
CH_3	CN	OAr	$C\equiv CR$
D	SO_2Ar	COOR	Ar
			$CH=CR_2$

pp. 228–230). Nevertheless, the following conclusions can be drawn from Table 3:

1. Inductive effects are fairly equal for *n*-alkyl groups of two or more carbons. Thus, an additional CH_2 does not cause much difference in a bond four bonds away or more.
2. For other groups, such as chloro-, the effect may be transmitted over a longer distance,[25] but in any case decreases with increasing distance.
3. Most groups are electron-withdrawing (called $-I$). The only electron-donating groups ($+I$) are alkyl groups, groups with a formal negative charge (but not even all of these), and atoms of low electronegativity, such as Si, Mg, etc. In Table 4 is a list of groups in approximate order of inductive effects. Deuterium is electron-donating with respect to hydrogen.[26] Other things being equal, atoms with *sp* bonding generally have a greater electron-withdrawing power than those with sp^2 bonding, which in turn have more electron-withdrawing power than those with sp^3 bonding.[27]

Bond Distances.[28] The distances between atoms in a molecule are characteristic properties of the molecule and can give us information if we compare the same bond in different molecules. The chief methods of determin-

---

[25] Inductive effects have been reported over unusually long distances. For example, see Peterson and Allen, *J. Am. Chem. Soc.* **85,** 3608 (1963); Schwartz, Hermánek, and Trojánek, *Chem. Ind.* (*London*) **1960,** 1212; Peterson, Casey, Tao, Agtarap, and Thompson, *J. Am. Chem. Soc.* **87,** 5163 (1965).

[26] Streitwieser and Klein, *J. Am. Chem. Soc.* **85,** 2759 (1963).

[27] Bent, *Chem. Rev.* **61,** 275–311 (1961), p. 281.

[28] For reviews on this subject and on bond angles, see Bent, Ref. 27; Cottrell and Sutton, *Quart. Rev.* (*London*) **2,** 260–276 (1948); Costain and Stoicheff, *J. Chem. Phys.* **30,** 777 (1959); and papers in *Tetrahedron* **17,** 125–266 (1962). For tables of bond distances and angles, see Tables of Interatomic Distances and Configurations in Molecules and Ions, *Chem. Soc.* (*London*), *Spec. Publ.* **11,** (1958); Interatomic Distances Supplement, *Chem. Soc.* (*London*), *Spec. Publ.* **18** (1965); Walsh, *Progr. Stereochem.* **1,** 1–35 (1954), pp. 10–23; Wheland, "Resonance in Organic Chemistry," pp. 165–167, John Wiley & Sons, Inc., New York, 1955; and Rogowski, *Fortschr. chem. Forsch.* **4,** 1–50 (1963), pp. 22–31.

TABLE 5. Bond distances in angstrom units
The values given are average lengths and do not necessarily apply *exactly* to the compounds mentioned

Bond type	*Length, Å*	*Typical compounds*		
C—C[38]				
sp^3—sp^3	1.54			
sp^3—sp^2	1.50	Acetaldehyde, toluene, propene		
sp^3—sp	1.46	Acetonitrile, propyne		
sp^2—sp^2	1.48	Butadiene, glyoxal, biphenyl		
sp^2—sp	1.43	Acrylonitrile, vinylacetylene		
sp—sp	1.38	Cyanoacetylene, butadiyne		
C═C[39]				
sp^2—sp^2	1.34	Ethylene		
sp^2—sp	1.31	Ketene, allenes		
sp—sp	1.28	Butatriene, carbon suboxide		
C≡C[39]				
sp—sp	1.205	Acetylene		
C—H[40]				
sp^3—H	1.11	Methane		
sp^2—H	1.10	Benzene, ethylene		
sp—H	1.08	HCN, acetylene		
C—O				
sp^3—O	1.41[41]	Dimethyl ether, ethanol		
sp^2—O	1.34[42]	Formic acid		
C═O				
sp^2—O	1.20[42]	Formaldehyde, formic acid		
sp—O	1.16[32]	CO_2		
C—N				
sp^3—N	1.47[43]	Methylamine		
sp^2—N	1.36[30]	Formamide		
C═N[44]				
sp^2—N	1.28	Oximes, imines		
C≡N[32]				
sp—N	1.16	HCN		
C—S[45]				
sp^3—S	1.81	Methyl mercaptan		
sp^2—S	1.75	Diphenyl sulfide		
C═S[45]				
sp—S	1.56	CS_2		
C—halogen	F[30]	Cl[30]	Br[46]	I[46]
sp^3—hal	1.38	1.78	1.94	2.14
sp^2—hal	1.35	1.73	1.85	2.07
sp—hal	1.27	1.63	1.79	1.99

ing bond distances and angles are x-ray diffraction (only for solids), electron diffraction (only for gases), and spectroscopic methods.[29] The distance between the atoms of a bond is not constant, since the molecule is always vibrating; and the measurements obtained are therefore average values, so that different methods give different results.[30] However, this must be taken into account only when fine distinctions are made.

Measurements vary in accuracy, but indications are that similar bonds have fairly constant lengths from one molecule to the next. The variation is generally less than 1%. Thus for a bond between two sp^3 carbons the following results have been found:

C—C *bond in*	*Bond length, Å*
Diamond	1.544[36]
C_2H_6	1.5324 ± 0.0011[31]
C_2H_5OH	1.55 ± 0.02[32]
C_2H_5Cl	1.5495 ± 0.0005[33]
Cyclohexane	1.540 ± 0.015[32]
tert-Butyl chloride	1.532[34]
n-Butane–*n*–heptane	1.531–1.534[35]

In Table 5 are given bond distances for some important bond types. As seen in Table 5, carbon bonds are shortened by increasing *s* character. This has usually been attributed to resonance and hyperconjugation (see p. 32), though more recently other explanations have been suggested.[37] The matter is still not completely settled.

Indications are that a C—D bond is slightly shorter than a corresponding C—H bond. Thus, electron-diffraction measurements of C_2H_6 and C_2D_6

---

[29] For surveys of methods, see Walsh, Ref. 28, pp. 1–9; and Speakman, *Progr. Stereochem.* **2,** 1–38 (1958).

[30] Lide, *Tetrahedron* **17,** 125 (1962).

[31] Bartell and Higginbotham, *J. Chem. Phys.* **42,** 851 (1965).

[32] Tables of Interatomic Distances, Ref. 28.

[33] Wagner and Dailey, *J. Chem. Phys.* **26,** 1588 (1957).

[34] Momany, Bonham, and Druelinger, *J. Am. Chem. Soc.* **85,** 3075 (1963); also see Lide and Jen, *J. Chem. Phys.* **38,** 1504 (1963).

[35] Bonham, Bartell, and Kohl, *J. Am. Chem. Soc.* **81,** 4765 (1959).

[36] Lonsdale, *Phil. Trans. Roy. Soc. London* **A240,** 219 (1947).

[37] For discussion, see Wilson, *Tetrahedron* **17,** 191 (1962).

---

[38] Somayajulu, *J. Chem. Phys.* **31,** 919 (1959).

[39] Costain and Stoicheff, *J. Chem. Phys.* **30,** 777 (1959).

[40] Bartell, Roth, Hollowell, Kuchitsu, and Young, *J. Chem. Phys.* **42,** 2683 (1965).

[41] Blukis, Kasai, and Myers, *J. Chem. Phys.* **38,** 2753 (1963).

[42] Kwei and Curl, *J. Chem. Phys.* **32,** 1592 (1960).

[43] Higginbotham and Bartell, *J. Chem. Phys.* **42,** 1131 (1965).

[44] Levine, *J. Chem. Phys.* **38,** 2326 (1963).

[45] Abrahams, *Quart. Rev. (London)* **10,** 407–436 (1956).

[46] Brown, *Trans. Faraday Soc.* **55,** 694 (1959).

showed a C—H bond distance of 1.1122 ± 0.0012 Å and a C—D distance of 1.1071 ± 0.0012 Å.[47]

Bond Angles. It might be expected that the bond angles of sp^3 carbon would always be the tetrahedral angle 109°28′, but this is so only where the four groups are identical, as in methane, neopentane, or carbon tetrachloride. In most cases the angles deviate a little from the pure tetrahedral value. For example, the C—C—Cr angle in 2-bromopropane is 114.2°.[48] Similarly, slight variations are generally found from the ideal values of 120 and 180° for sp^2 and sp carbon, respectively.[9] So far, no correlation has been found between these variations and, say, increasing s character.[29] Of course, in strained molecules the bond angles may be greatly distorted from the ideal values (see p. 116).

For oxygen, an angle of 90° would be predicted from p^2 bonding, and 109°28′ from sp^3 bonding. The measured angles are much closer to the sp^3 value, as shown in Table 6. Sulfur angles are less than those for corresponding oxygen compounds, but as Table 6 shows, the pattern of increasing size with substitution of carbon for hydrogen is found here too. The bond angles of nitrogen increase much less with alkylation (Table 6).

Bond Energies.[49] There are two kinds of bond energy. The energy necessary to cleave a bond to give the constituent radicals is called the *dissociation*

---

[47] Bartell and Higginbotham, *J. Chem. Phys.* **42**, 851 (1965).

[48] Schwendeman and Tobiason, *J. Chem. Phys.* **43**, 201 (1965).

[49] For reviews including methods of determination, see Kerr, *Chem. Rev.* **66**, 465–500 (1966); Szwarc, *Chem. Rev.* **47**, 75–173 (1950), *Quart. Rev.* (*London*) **5**, 22–43 (1951); Knox and Palmer, *Chem. Rev.* **61**, 247–255 (1961); Benson, *J. Chem. Educ.* **42**, 502–518 (1965); and Cottrell, "The Strengths of Chemical Bonds," 2d ed., Academic Press Inc., New York, 1958.

TABLE 6. Oxygen, sulfur, and nitrogen bond angles in some compounds

Angle	*Value*	*Compound*	*Ref.*
H—O—H	104°27′	Water	5
C—O—H	107–109°	Methanol	32
C—O—C	111°43′	Dimethyl ether	41
C—O—C	124 ± 5°	Diphenyl ether	45
H—S—H	92.1°	H_2S	45
C—S—H	99.4°	Methyl mercaptan	45
C—S—C	109°	*p*-Tolyl sulfide	45
H—N—H	106°46′	Ammonia	5
H—N—H	106°	Methylamine	50
C—N—H	112°	Methylamine	50
C—N—C	108.7°	Trimethylamine	51

[50] Lide, *J. Chem. Phys.* **27**, 343 (1957).

[51] Lide and Mann, *J. Chem. Phys.* **28**, 572 (1958).

$$\begin{array}{rcll r}
C_2H_{6\,(gas)} + 3\tfrac{1}{2}O_{2\,(gas)} & = & 2CO_{2\,(gas)} & + 3H_2O_{(liq.)} & +372.9\ \text{kcal} \\
2CO_{2\,(gas)} & = & 2C_{(graphite)} & + 2O_{2\,(gas)} & -188.2\ \text{kcal} \\
3H_2O_{(liq.)} & = & 3H_{2\,(gas)} & + 1\tfrac{1}{2}O_{2\,(gas)} & -204.9\ \text{kcal} \\
3H_{2\,(gas)} & = & 6H_{(gas)} & & -312.5\ \text{kcal} \\
2C_{(graphite)} & = & 2C_{(gas)} & & -343.4\ \text{kcal} \\
\hline
C_2H_{6\,(gas)} & = & 6H_{(gas)} & + 2C_{(gas)} & -676.1\ \text{kcal}
\end{array}$$

Figure 13. *Calculation of the heat of atomization of ethane at 25° C.*

energy and is designated **D**. For example, **D** for $H_2O \longrightarrow HO + H$ is 118 kcal/mole. However, this is not taken as the energy of the O—H bond in water, since **D** for $H—O \longrightarrow H + O$ is 100 kcal/mole. The average of these two values, 109 kcal/mole, is taken as the *bond energy* and designated **E**. In diatomic molecules, of course, **D** = **E**. It is the **E** values that organic chemists are primarily interested in and that we shall be primarily concerned with.

D values may be easy or difficult to measure, but there is no question as to what they mean. With **E** values the matter is not so simple. For methane, the total energy of conversion from CH_4 to C + 4H (at 0° K) is 393 kcal/mole.[52] Consequently, **E** for the C—H bond in methane is 98 kcal/mole at 0° K. The more usual practice, though, is not to measure the heat of atomization (that is, the energy necessary to convert a compound to its atoms) directly, but to calculate it from the heat of combustion. Such a calculation is shown in Figure 13.

Heats of combustion are very accurately known for hydrocarbons. For methane the value is 212.8 kcal/mole (at 25°C), which leads to a heat of atomization of 398.0 kcal/mole (at 25°), or a value of **E** for the C—H bond of 99.5 kcal/mole at 25°. This method is fine for molecules like methane in which all the bonds are equivalent, but for more complicated molecules assumptions must be made. Thus for ethane, the heat of atomization of 25° is 676.1 kcal/mole (Figure 13), and we must decide how much of this energy is due to the C—C bond, and how much to the six C—H bonds. Any assumption must be artificial, since there is no way of actually obtaining this information, and indeed the question has no real meaning. If we make the assumption that **E** for each of the C—H bonds is the same as **E** for the C—H bond in methane (99.5 kcal/mole), then $6 \times 99.5 = 597.0$, leaving 79.1 kcal/mole for the C—C bond. However, a similar calculation for propane gives a value of 80.3 for the C—C bond, and for isobutane, the value is 81.6. A consideration of heats of atomization of isomers also illustrates the difficulty. **E** values for the C—C bonds in pentane, isopentane, and neopentane, calculated from heats of atomization in the same way, are (at 25°) 81.1, 81.8, and 82.4 kcal/mole, respectively, even though all of them have 12 C—H bonds and 4 C—C bonds.

---

[52] For the four steps, **D** values are 101–102, 88, 124, and 80 kcal/mole, respectively, though the middle values are much less reliable than the other two. Knox and Palmer, *Chem. Rev.* **61**, 247–255 (1961); Brewer and Kester, *J. Chem. Phys.* **40**, 812 (1964).

These differences have been attributed to various factors caused by the introduction of new structural features. Thus isopentane has a tertiary carbon whose C—H bond does not have exactly the same amount of *s* character as the C—H bond in pentane, which for that matter contains secondary carbons not possessed by methane. It is known that **D** values, which *can* be measured, are not the same for primary, secondary, and tertiary C—H bonds (see Table 1, in Chapter 5, p. 155). There is also the steric factor. Hence it

TABLE 7. Bond-energy (E) values for some important bond types
E values (in kilocalories per mole at 25°) are arranged within each group in order of decreasing strength. The mean values are averaged over a large series of compounds. The calculated values are computed for just one compound using values for other bonds from earlier values in the table

Bond	*Mean value*[53]	*Value calc. from*	
O—H	110–111	110.6	H_2O
C—H	96–99	99.5	CH_4
N—H	93	93.4	NH_3
S—H	82	83	H_2S
C—F	....	116	CF_4
C—H	96–99	99.5	CH_4
C—O	85–91	76.8 84.2	CH_3OH C_2H_5OH
C—C	83–85	79.1	C_2H_6
C—Cl	79	78.3	CCl_4
C—N	69–75[54]	66.5	CH_3NH_2
C—Br	66	69 65	CBr_4 $CHBr_3$
C—S	66	64	C_2H_5SH
C—I	52	50.1	CH_3I
C≡C	199–200	194.4	C_2H_2
C=C	146–151	141.3	C_2H_4
C—C	83–85	79.1	C_2H_6
C≡N	204	206.1	HCN
C=O	173–81	164 192	HCHO CO_2
C=N	143[54]		
C=S	....	132	CS_2

---

[53] These values, except where noted, are from Lovering and Laidler, *Can. J. Chem.* **38**, 2367 (1960); and Levi and Balandin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1960**, 149.

[54] Bedford, Edmondson, and Mortimer, *J. Chem. Soc.* **1962**, 2927.

is certainly not correct to use the value of 99.5 from methane as the **E** value for all C—H bonds. Several empirical equations have been devised which account for these factors; from these the total energy can be computed[55] if the proper set of parameters (one for each structural feature) is inserted. Of course these parameters are originally calculated from the known total energies of some molecules which contain the structural feature.

In Table 7 are given **E** values for various bonds. The mean values given are those averaged over a large series of compounds. The other values are calculated for just one compound, using values for the other bonds from earlier values in the table. The literature contains charts which take account of hybridization (thus an sp^3 C—H bond does not have the same energy as an sp^2 C—H bond).[56]

---

[55] For a review, see Skinner and Pilcher, *Quart. Rev.* (*London*) **17**, 264–288 (1963).

[56] Ref. 55; Cox, *Tetrahedron* **18**, 1337 (1962).

CHAPTER TWO

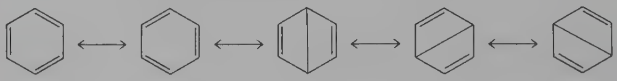
Delocalized Chemical Bonding

Although the bonding of many compounds can be adequately described by a single Lewis structure (p. 15), this is not sufficient for many other compounds. These compounds contain one or more bonding orbitals which are not restricted to two atoms, but which are spread out over three or more. Such bonding is said to be *delocalized.*[1] In this chapter we shall see which types of compounds must be represented in this way.

The two chief methods of approximately solving the wave equation, discussed in Chapter 1, are also used for compounds containing delocalized bonds.[2] In the valence-bond method several possible Lewis structures, called *canonical forms,* are drawn, and the molecule is taken to be a weighted average of them. Each ψ in Eq. 14, Chapter 1 (p. 9),

$$\Psi = c_A\psi_A + c_B\psi_B + \cdots$$

represents one of these structures. This representation of a real structure as a weighted average of two or more canonical forms is called *resonance.* For benzene the canonical forms are **1** and **2**.



1 **2** **3** **4** **5**

Double-headed arrows are used to indicate resonance. When the wave equation is solved, it is found that the energy value obtained by considering **1** and **2** to participate equally is lower than that for **1** or **2** alone, and if **3**, **4**, and **5** (called *Dewar structures*) are also considered, the value is lower still. According to this method, **1** and **2** each contribute 39% to the actual molecule, and the others 7.3% each.[3] The carbon-carbon bond order is 1.463—not 1.5, which would be the case if only **1** and **2** contributed. The *bond order* of a particular bond, in the valence-bond method, is the sum of the weights of those canonical forms in which the bond is double, plus 1 for the single bond which is present in all of them.[4] Thus, according to this picture, each C—C bond is not halfway between a single and a double bond, but somewhat less. The energy of the actual molecule is obviously less than that of any one Lewis structure, since otherwise it would have one of those structures. The difference in energy between the actual molecule and the Lewis structure of lowest energy[5] is called the *resonance energy.*

---

[1] For a definitive treatment of delocalization, see Wheland, "Resonance in Organic Chemistry," John Wiley & Sons, Inc., New York, 1955.

[2] There are other methods. For a discussion of the free-electron method, see Streitwieser, "Molecular Orbital Theory for Organic Chemists," pp. 27–29, John Wiley & Sons, Inc., New York, 1961. For the nonpairing method, in which benzene is represented as having three electrons between adjacent carbons, see Hirst and Linnett, *J. Chem. Soc.* **1962**, 1035.

[3] Pullman and Pullman, *Progr. Org. Chem.* **4**, 31–71 (1958), p. 33.

[4] For a more precise method of calculating valence-bond bond orders, see Clarkson, Coulson, and Goodwin, *Tetrahedron* **19**, 2153 (1963).

Qualitatively, the resonance picture is often used to describe the structure of molecules, but quantitative valence-bond calculations become much more difficult as the structures become more complicated (e.g., naphthalene, pyridine, etc.). Therefore the molecular-orbital method is more often used for the solution of wave equations. If we look at benzene by this method (qualitatively), we see that each carbon atom, being connected to three other atoms, uses sp^2 orbitals to form σ bonds, so that all 12 atoms are in one plane. Each carbon has a p orbital (containing one electron) remaining, and each of these can overlap equally with the two adjacent p orbitals. This overlap of six orbitals (see Figure 1) produces six new orbitals, of which three (shown) are bonding. These three (called π orbitals) all occupy approximately the same space. They each have the plane of the ring as a node, and so are in two parts, one above and one below the plane. The two orbitals of higher energy (Figure 1*b* and *c*) also have another node. The six electrons which occupy this torus-shaped cloud are called the *aromatic sextet.* The carbon-carbon bond order for benzene, calculated by the molecular-orbital method, is 1.667.[6]

Although the valence-bond and molecular-orbital methods give slightly different results, both of them show that there is delocalization in benzene. For example, each predicts that the six carbon-carbon bonds should have equal lengths, which is true. Since each method is useful for certain purposes, we shall use one or the other, as appropriate.

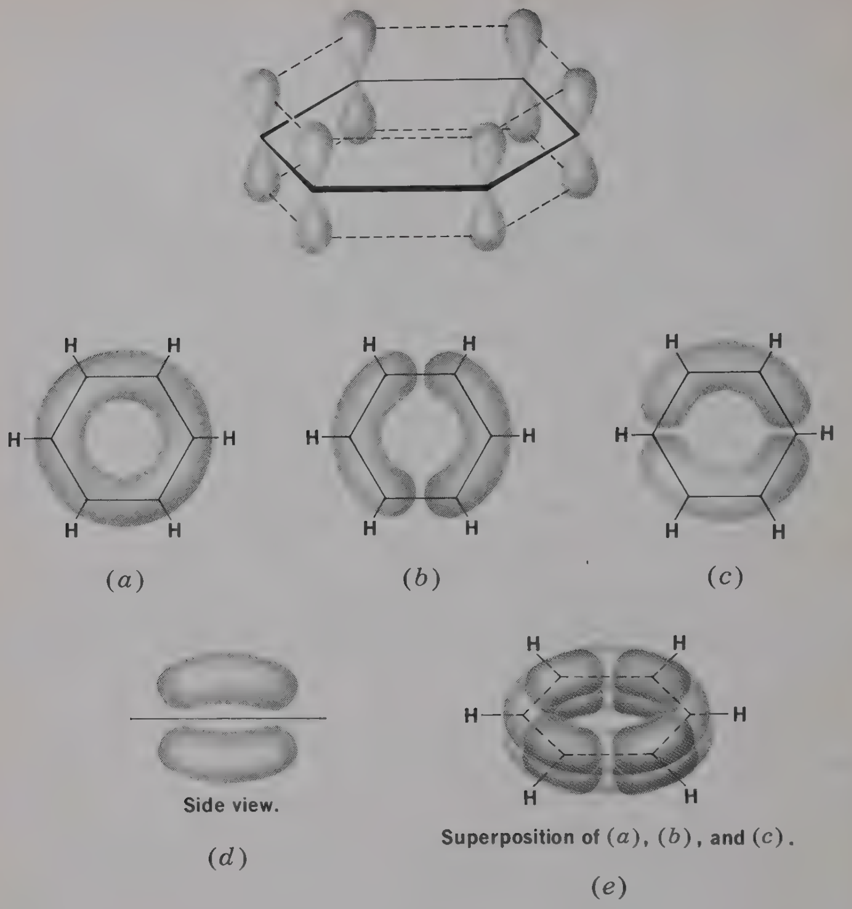
Bond Distances and Energies in Compounds Containing Delocalized Bonds. If we add the energies of all the bonds in benzene, taking the values from a table like Table 7 in Chapter 1 (p. 26), the value for the heat of atomization turns out to be less than that actually found in benzene (Figure 2). The actual value is 1323 kcal/mole. If we use **E** values for a C=C double bond obtained from cyclohexene (148.8), for a C—C single bond from cyclohexane (81.8), and for C—H bonds from methane (99.5), we get a total of 1289 kcal/mole for structure **1** or **2**. The resonance energy by this calculation is therefore 34 kcal/mole. Of course, this is an arbitrary calculation since, in addition to the fact that we are calculating a heat of atomization for a nonexistent structure (**1**), we are forced to use **E** values, which themselves do not have a firm basis in reality. The resonance energy can never be measured, only estimated, since we can measure the heat of atomization of the real molecule, but can only make an intelligent guess as to that of the Lewis structure of lowest energy. The generally accepted value for the resonance energy of benzene is 36 kcal/mole, and by any calculation the real molecule is more stable than a hypothetical **1** or **2**.

The energies of the six benzene orbitals can be calculated from molecular-orbital theory in terms of two quantities, α and β. The quantity α is the amount of energy possessed by an isolated $2p$ orbital before overlap, while β (called the *resonance integral*) is an energy unit expressing the degree

---

[5] Of course, the Lewis structures are not real, and their energies can only be estimated.

[6] The molecular-orbital method of calculating bond order is more complicated than the valence-bond method. See Ref. 3, p. 36, and Ref. 4.



(*a*) (*b*) (*c*)

Side view.

(*d*)

Superposition of (*a*), (*b*), and (*c*).

(*e*)

Figure 1. *The six p orbitals of benzene overlap to form three bonding orbitals. (a) to (c) are top views of these three; (d) is a side view of any of them; (e) shows the three superimposed.*

of stabilization resulting from π-orbital overlap. A negative value of β corresponds to stabilization, and the energies of the six orbitals are (lowest to highest): $\alpha + 2\beta$; $\alpha + \beta$; $\alpha + \beta$; $\alpha - \beta$; $\alpha - \beta$; and $\alpha - 2\beta$.[7] The total energy of the three occupied orbitals is $6\alpha + 8\beta$, since there are two electrons in each orbital. The energy of an ordinary double bond is $\alpha + \beta$, so that structure **1** or **2** would have an energy of $6\alpha + 6\beta$. The resonance energy of benzene is therefore 2β. Unfortunately, there is no convenient way to calculate the value of β from molecular-orbital theory, and it is often given (for benzene)

---

[7] For the method of calculating these results and similar results given in this chapter, see Higasi, Baba, and Rembaum, "Quantum Organic Chemistry," Interscience Publishers, Inc., New York, 1965; and Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, 1961.

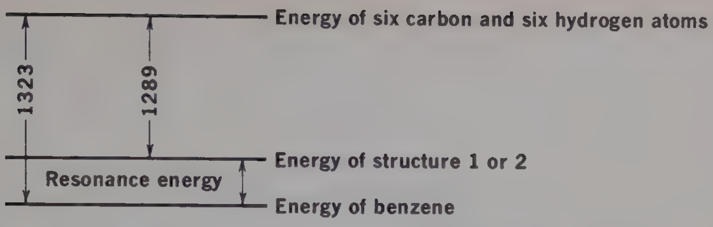

Energy of six carbon and six hydrogen atoms
1323
1289
Energy of structure 1 or 2
Resonance energy
Energy of benzene

Figure 2. *Resonance energy in benzene (in kilocalories per mole).*

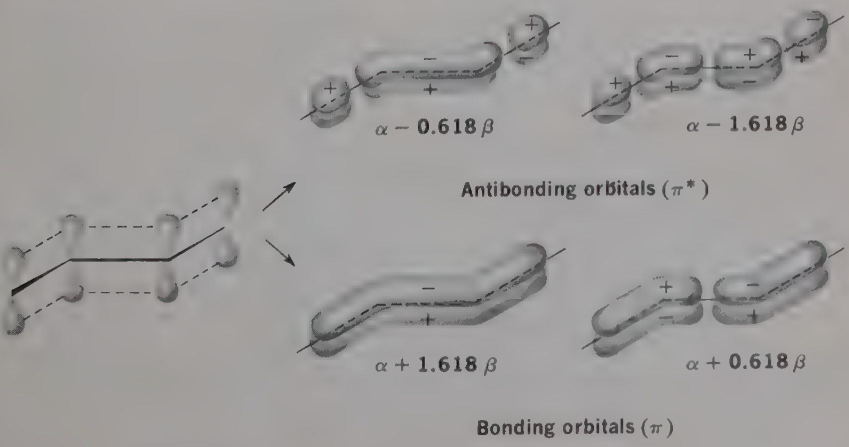
as about 18 kcal/mole, this number being half of the resonance energy calculated from heats of combustion.

We might expect that bond distances in compounds exhibiting delocalization would lie between the values given in Table 5 in Chapter 1 (p. 22). For benzene this is certainly the case, since the carbon-carbon bond distance is 1.39 Å, which is between the 1.48 Å for an sp^2-sp^2 C—C single bond and the 1.34 Å of the sp^2-sp^2 C═C double bond.

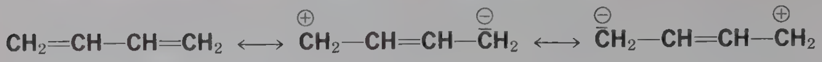
Kinds of Molecules Which Have Delocalized Bonds. There are three main types of structure that exhibit delocalization:

1. *Double (or triple) bonds in conjugation.* Benzene is, of course, an example, but the simplest is butadiene. In the molecular-orbital picture (Figure 3) the overlap of four orbitals gives two bonding orbitals, which contain the four electrons, and two vacant antibonding orbitals. It may be seen that each orbital has one more node than the one of next lower energy. The energies of the four orbitals are (lowest to highest): $\alpha + 1.618\beta$; $\alpha + 0.618\beta$; $\alpha - 0.618\beta$; and $\alpha - 1.618\beta$; hence the total energy of the two occupied orbitals is $4\alpha + 4.472\beta$. Since the energy of two isolated double bonds is $4\alpha + 4\beta$, the resonance energy by this calculation is 0.472β.

Figure 3. *The four π orbitals of butadiene, formed by overlap of four p orbitals.*



In the resonance picture, these structures are considered to contribute:



$$\underset{\mathbf{6}}{CH_2{=}CH{-}CH{=}CH_2} \longleftrightarrow \underset{\mathbf{7}}{\overset{\oplus}{C}H_2{-}CH{=}CH{-}\overset{\ominus}{\bar{C}}H_2} \longleftrightarrow \underset{\mathbf{8}}{\overset{\ominus}{\bar{C}}H_2{-}CH{=}CH{-}\overset{\oplus}{C}H_2}$$

By either picture the bond order of the central bond should be higher than 1, and that of the other carbon-carbon bonds less than 2, although neither predicts that the three bonds have equal electron density. Molecular-orbital bond orders of 1.894 and 1.447 have been calculated.[8]

In recent years doubt has been cast on the reality of delocalization in butadiene and similar molecules. Thus, the bond lengths in butadiene are 1.34 Å for the double bonds and 1.48 Å for the single bond.[9] These, within 0.01 Å, are the lengths expected without considering delocalization (Table 5 of Chapter 1, p. 22). Also, resonance energies, calculated from heats of combustion, turn out to be quite low. The resonance energy for butadiene is about 4 kcal/mole, using comparison values from butane and 1-butene. Incidentally, this means that β for this compound is about 8 kcal/mole. A better system for calculation is 1,3-pentadiene, since it can be compared with 1,4-pentadiene, which also has two double bonds, two carbon-carbon single bonds, and eight C—H bonds:

1,4-pentadiene

2 **C═C** (from 1-pentene):	2 × 146.1	292.2 kcal/mole
2 **C—C** (from pentane):	2 × 81.0	162.0
8 **C—H**:	8 × 99.5	796.0
		1250.2
Actual value		1250.0
Resonance energy		−0.2

cis-1,3-pentadiene

C═C (from 1-pentene):	146.1 kcal/mole
C═C (from *cis*-2-pentene):	147.8
2 **C—C** (as above):	162.0
8 **C—H** (as above):	796.0
	1251.9
Actual value	1256.5
Resonance energy	4.6

trans-1,3-pentadiene

C═C (from 1-pentene):	146.1 kcal/mole
C═C (from *trans*-2-pentene):	148.7
2 **C—C** (as above):	162.0
8 **C—H** (as above):	796.0
	1252.8
Actual value	1256.6
Resonance energy	3.8

---

[8] Coulson, *Proc. Roy. Soc.* (*London*) **A169**, 413 (1939).

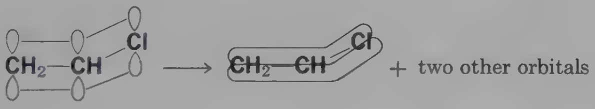
[9] Marais, Sheppard, and Stoicheff, *Tetrahedron* **17**, 163 (1962).

These results are consistent with a value of about 4 kcal/mole for butadiene. Nevertheless, if differences in hybridization are taken into account, 1,3- and 1,4-pentadiene are not strictly comparable. The former has three sp^3 C—H and five sp^2 C—H bonds, while the latter has two and six, respectively. Also, the two single C—C bonds of the 1,4-diene are both sp^2-sp^3 bonds, while in the 1,3-diene, one is sp^2-sp^3, and the other is sp^2-sp^2. Therefore, it may be that some of the already small value of 4 kcal/mole is not resonance energy but arises from differing energies of bonds of different hybridization.[10]

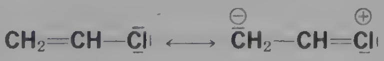
Although bond distances fail to show it, and the resonance energy is low, the fact that butadiene is planar[11] shows that there is some delocalization, even if not so much as previously thought.

Similar delocalization is found in other conjugated systems, such as $C{=}C{-}C{=}O$ and $C{\equiv}C{-}C{=}N$, and in longer systems, with three or more multiple bonds in conjunction.

2. *Double (or triple) bonds in conjugation with a p orbital on an adjacent atom.* It is a general rule that, when n atomic orbitals overlap, n molecular orbitals are created. Overlap of a p orbital with an adjacent double bond gives rise to three molecular orbitals. There are three cases: the p orbital may contain two, one, or no electrons. A typical example of the former is vinyl chloride:



In this case, although the p orbital of the chlorine is filled, it still overlaps with the double bond. The four electrons occupy the two molecular orbitals of lowest energies. This is our first example of resonance involving overlap between unfilled orbitals and a *filled* orbital. Resonance forms for vinyl chloride are



$$CH_2{=}CH{-}\underline{\overline{Cl}}| \longleftrightarrow \overset{\ominus}{\bar{C}H_2}{-}CH{=}\overset{\oplus}{\underline{Cl}}|$$

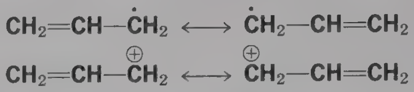
Any system containing an atom which has an unshared pair and which is directly attached to a multiple-bond atom can show this type of delocalization.

The other two cases are generally found only in carbonium ions and free radicals. Thus the allyl free radical and allyl cation have double bonds in conjugation with, respectively, an unpaired electron and an empty orbital (see Chapter 5):

---

[10] For negative views on delocalization in butadiene and similar molecules, see Dewar and Gleicher, *J. Am. Chem. Soc.* **87,** 692 (1965); Dewar and Schmeising, *Tetrahedron* **5,** 166 (1959), **11,** 96 (1960); Dewar, *Tetrahedron* **19,** Suppl. 2, 89 (1963); Brown, *Trans. Faraday Soc.* **55,** 694 (1959); Somayajulu, *J. Chem. Phys.* **31,** 919 (1959); Mikhailov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1960,** 1284. For positive views, see Berry, *J. Chem. Phys.* **30,** 936 (1962); and Kogan and Popov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964,** 1306. In general, the negative argument is that resonance involving excited structures, such as **7** and **8,** is unimportant. See rule 6 on page 35.

[11] See Ref. 9. See discussion of this in Bastiansen and Trætteberg, *Tetrahedron* **17,** 147 (1962); Fischer-Hjalmars, *Tetrahedron* **17,** 235 (1962); **19,** 1805 (1963); and Coulson, *Tetrahedron* **17,** 258 (1962).



$$CH_2{=}CH{-}\dot{C}H_2 \longleftrightarrow \dot{C}H_2{-}CH{=}CH_2$$

$$CH_2{=}CH{-}\overset{\oplus}{C}H_2 \longleftrightarrow \overset{\oplus}{C}H_2{-}CH{=}CH_2$$

In these cases also, there are three molecular orbitals, the one of lowest energy being filled. In the cation the others are empty, while one electron resides in the middle orbital of the radical.

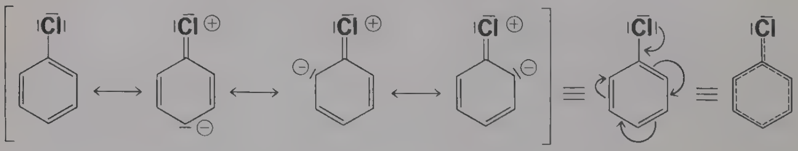
3. *Hyperconjugation.* The third type of delocalization is called *hyperconjugation,* and is discussed on page 56.

We shall find examples of delocalizations which cannot be strictly classified as belonging to any of these types.

The Rules of Resonance. We have seen that one way of expressing the actual structure of a molecule containing delocalized bonds is to draw several possible structures and to assume that the actual molecule is a hybrid of these. These canonical forms have no existence except in our imagination. The molecule does *not* rapidly shift between them. It is *not* the case that some molecules have one canonical form and some another. All the molecules of the substance have the same structure. That structure is always the same all the time and is a weighted average of all the canonical forms. In drawing canonical forms and in deriving the true structures from them, we are guided by certain rules, among them:

1. All the canonical forms must be bona fide Lewis structures (see p. 15). For instance, in none of them may carbon have five bonds.

2. The positions of the nuclei must be the same in all the structures. This means that all we are doing when we draw the various canonical forms is putting the *electrons* in in different ways. For this reason, shorthand ways of representing resonance are easy to devise:



9 **10**

The resonance interaction of chlorine with the benzene ring may be represented as shown in **9** or **10**, and either of these representations is often used to save space. However, we shall not use the curved-arrow method of **9**, since in this book arrows will be used to express actual movement of electrons in reactions. We shall use representations like **10**, or else write out the canonical forms. The convention used in dotted-line formulas like **10** is that bonds which are present in all canonical forms are drawn as solid lines, while bonds which are not present in all forms are drawn as dotted lines. In most resonance, σ bonds are not involved, and only the π or unshared electrons are put in in different ways.

3. All atoms taking part in the resonance (that is, covered by delocalized electrons) must lie in a plane, or nearly so (see p. 36). This, of course, does not apply to atoms which have the same bonding in all the canonical forms. The reason for planarity is maximum overlap of the *p* orbitals.

4. All canonical forms must have the same number of unpaired electrons. Thus $\dot{C}H_2—CH{=}CH—\dot{C}H_2$ is not a valid canonical form for butadiene.

5. The energy of the actual molecule is lower than that of any form, obviously. Therefore, delocalization is a stabilizing phenomenon. Many species which would not be expected to be stable solely on the basis of the Lewis structure of lowest energy turn out to be stable because of the resonance.

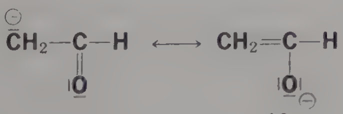
6. All canonical forms do not contribute equally to the true molecule. Each form contributes in proportion to its stability, the most stable form contributing most. Thus, for ethylene, the form $\overset{-}{C}H_2—\overset{+}{C}H_2$ has such a high energy compared to $CH_2{=}CH_2$ that it essentially does not contribute at all. We have seen the argument that such structures do not contribute even in such cases as butadiene.[10] Equivalent canonical forms, such as **1** and **2,** contribute equally. The greater the number of significant structures that can be written, and the more nearly equal they are, the greater the resonance energy, other things being equal.

It is not always easy to decide relative stabilities of imaginary structures, and the chemist is often guided by his intuition. However, the following rules may be helpful:

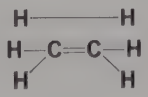
1. Structures with more covalent bonds are ordinarily more stable than those with fewer.

2. Stability is decreased by an increase in charge separation. However, when the compound is dissolved in different solvents, ionic structures make a greater contribution in the more polar solvent.[12]

3. Structures which carry a negative charge on a more electronegative atom are more stable than those in which the charge is on a less electronegative atom. Thus, **12** is more stable than **11**. Similarly, positive charges are best carried on atoms of low electronegativity.



11 **12**



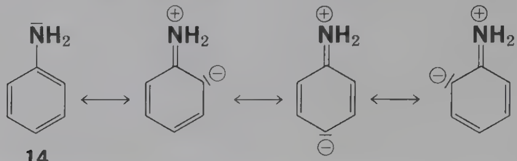
13

4. Structures with distorted bond angles or lengths are unstable, e.g., the structure **13,** for ethane.

The Resonance Effect. Resonance always results in a different distribution of electron density than would be the case if there were no resonance. For example, if **14** were the actual structure of aniline, then the two unshared electrons of the nitrogen would reside entirely on that atom. Since the real structure is not **14** but a hybrid which includes contributions from the other canonical forms shown, the electron density of the unshared pair does not reside entirely on the nitrogen, but is spread over the ring. This decrease in

---

[12] Taft, Glick, Lewis, Fox, and Ehrenson, *J. Am. Chem. Soc.* **82,** 756 (1960).

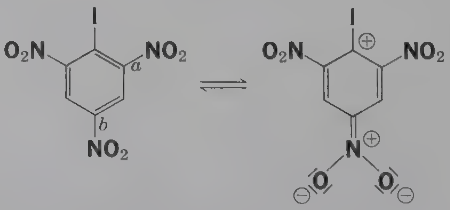


14

electron density at one position (and corresponding increase elsewhere) is called the *resonance,* or *mesomeric, effect.* We loosely say that the NH_2 contributes or donates electrons to the ring by a resonance effect, although no actual contribution has taken place. The "effect" is caused by the fact that the electrons are in a different place from that which we should expect if there were no resonance. In ammonia, where resonance is absent, the unshared pair *is* located on the nitrogen atom. As with the inductive effect (p. 19), we may think of a certain molecule (in this case ammonia) as a substrate and then see what happens to the electron density when we make a substitution. When one of the hydrogen atoms of the ammonia molecule is replaced by a benzene ring, the electrons are "withdrawn" by the resonance effect, just as, when a methyl group replaces a hydrogen of benzene, electrons are "donated" by the inductive effect of the methyl. The idea of donation or withdrawal merely arises from the comparison of a compound with a closely related one, or of a real compound with a canonical form.

Steric Hindrance to Resonance. In rule 3 (p. 35), it was stated that all the atoms covered by delocalized electrons must lie in a plane, or nearly so. Many examples are known where resonance is reduced or prevented because the atoms are sterically forced out of planarity.

Bond lengths for the *o*- and *p*-nitro groups in picryl iodide are quite different.[13]



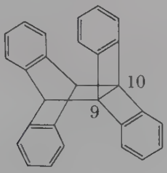
Distance *a* is 1.45 Å, whereas *b* is 1.35 Å. The obvious explanation is that the oxygens of the *p*-nitro group are in the plane of the ring, and thus in resonance with it, so that *b* has partial double-bond character, while the oxygens of the *o*-nitro groups are forced out of the plane by the large iodine atom.

---

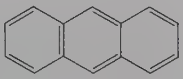
[13] Wepster, *Progr. Stereochem.* **2**, 99–156 (1958), p. 125.

Another example is 2,3-di-*tert*-butylbutadiene, which is a stable, *nonconjugated* diene.[14] The double bonds are not in the same plane but are forced out by the large *tert*-butyl groups.

The Dewar-type structure for the central ring of the anthracene system in **15** is possible only because the 9,10-substituents prevent the system from being planar.[15] **15** is the actual structure of the molecule, and it is not in resonance with forms such as **16**, though in anthracene itself, Dewar structures and structures like **16** both contribute. This is a consequence of rule 2 (p. 34). In order for a **16**-like structure to contribute to resonance in **15**, the nuclei would have to be in the same positions in both forms.

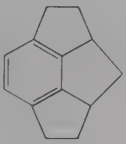


15

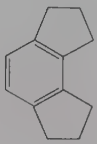


16

Even the benzene ring may be forced out of planarity.[16] Thus, **17** absorbs oxygen on standing and is easily hydrogenated, although **18** is almost completely unreactive.[17]



17



18

AROMATICITY

It was recognized in the nineteenth century that aromatic compounds differed greatly from aliphatic ones; but for many years chemists were hard pressed to arrive at a mutually satisfactory definition of aromatic character.[18] Qualitatively, there has never been real disagreement. Definitions have taken the form that aromatic compounds are characterized by a special stability and that they undergo substitution reactions more easily than addition reactions. The difficulty arises because these definitions are vague, and not easy to apply in borderline cases. With the advent of the technique of nuclear magnetic resonance, it is now possible to determine experimentally whether or not a compound has a closed ring of electrons; and aromaticity may now be defined as the ability to sustain an induced ring current.[19, 20] Aromatic compounds are thus the arch-examples of delocalized bonding. It should be emphasized that the old and new definitions are not necessarily parallel. If a compound has a closed electron ring (and is therefore aromatic under the new definition), it is more stable than the canonical form of lowest energy, but this does not mean that it will be in fact stable to air, light, or common reagents, since *this* stability is determined not by the resonance energy, but by the difference in free energy between the actual molecule and the transition states for the reactions involved; and these differences may be quite small, even if the resonance energy is large.

---

[14] Wynberg, DeGroot, and Davies, *Tetrahedron Letters* **1963**, 1083.

[15] Applequist and Searle, *J. Am. Chem. Soc.* **86**, 1389 (1964).

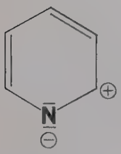
[16] For a review of planarity in aromatic systems, see Ferguson and Robertson, *Advan. Phys. Org. Chem.* **1**, 203–281 (1963).

[17] Rapoport and Smolinsky, *J. Am. Chem. Soc.* **82**, 1171 (1960).

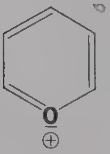
[18] For a monograph on nonbenzenoid aromatic compounds, see Ginsburg, "Non-Benzenoid Aromatic Compounds," Interscience Publishers, Inc., New York, 1959. For reviews, see Vol'pin, *Russ. Chem. Rev.* **29**, 129–160 (1960); Baker, in Todd, "Perspectives in Organic Chemistry," pp. 28–67, Interscience Publishers, Inc., New York, 1956; Baker and McOmie, *Progr. Org. Chem.* **3**, 44–80 (1955); and Hafner, *Angew. Chem. Intern. Ed. Engl.* **3**, 165–173 (1964).

The vast majority of aromatic compounds have six electrons in a ring (the aromatic sextet), and these compounds will be considered first.

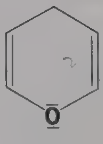
Six-membered Rings. Not only is the benzene ring aromatic, but so are many heterocyclic analogs in which one or more hetero atoms replace carbon in the ring. When nitrogen is the hetero atom, little difference is made in the sextet, and the unshared pair of the nitrogen does not participate in the aromaticity. Therefore, derivatives such as N-oxides or pyridinium ions are still aromatic. However, for nitrogen heterocyclics there are more canonical forms (for example, **19**) than in benzene. Where oxygen or sulfur is the hetero atom, it must be present in its ionic form (**20**) in order to possess the valence of three that participation in such a system demands. Thus, pyran (**21**) is not aromatic, but the pyrylium ion (**20**) is. Six-membered aromatic rings are known which contain no carbon at all, e.g., borazoles (**22**) and phosphonitriles (**23**).[21]



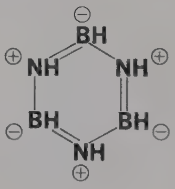
19



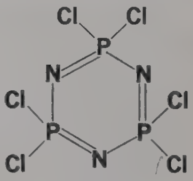
20



21



22



23

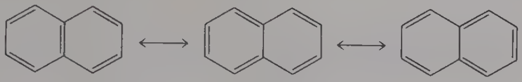
---

[19] On p. 193 will be found a discussion of how ring currents are detected by nuclear magnetic resonance.

[20] It has been maintained that ring currents are not real and that "any suggestion that 'aromaticity'—whatever that word may mean—be defined in terms of the ability of a molecule to sustain a ring current must be considered unreasonable." [Musher, *J. Chem. Phys.* **43**, 4083 (1965).] However, the interpretation of a large number of nuclear-magnetic-resonance spectra is consistent with the idea of ring currents.

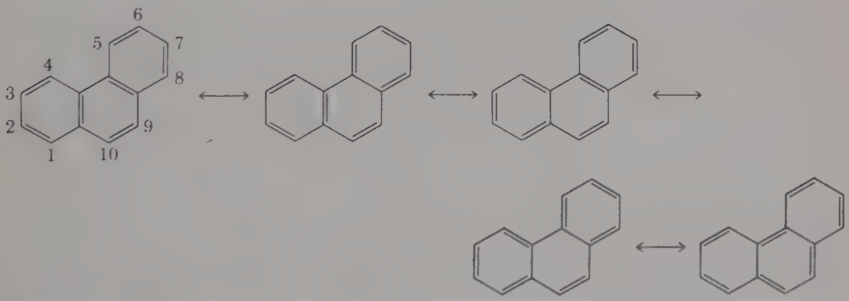
[21] For a review of phosphonitriles, see Shaw, Fitzsimmons, and Smith, *Chem. Rev.* **62**, 247–281 (1962).

In systems of fused six-membered aromatic rings,[22] the principal canonical forms are usually not all equivalent. **24** has a central double bond and is thus different from the other two canonical forms of naphthalene, which are equivalent to each other:



24

For naphthalene, these are the only forms that can be drawn without consideration of Dewar forms or those with charge separation. If we assume that these contribute equally, then the 1,2-bond has more double-bond character than the 2,3-bond. In agreement with this prediction, the 1,2- and 2,3-bond distances are 1.36 and 1.415 Å, respectively,[23] and ozone preferentially attacks the 1,2-bond.[24] This nonequivalency of bonds is called *partial bond fixation*[25] and is found in nearly all fused aromatic systems. In phenanthrene, where the 9,10-bond is a single bond in only one of five forms, bond fixation becomes extreme, and this bond is readily attacked by many reagents:



The resonance energies of fused systems increase as the number of principal canonical forms increases, as predicted by rule 6 (p. 35). Thus, for benzene, naphthalene, anthracene, and phenanthrene, for which we can draw, respectively, two, three, four, and five principal canonical forms, the resonance energies are, respectively, 36, 61, 84, and 92 kcal/mole, calculated from heat-of-combustion data.[26]

Not all fused systems can be fully aromatic. Thus for phenalene (**25**) there is no way in which double bonds may be distributed so that each carbon has one single and one double bond.[27] However, phenalene is acidic, and reacts with potassium methoxide to give the corresponding anion (**26**), which is completely aromatic. So also are the corresponding free-radical and cation, in which the resonance energies are the same (see p. 47).[28]

---

[22] For a treatise, see Clar, "Polycyclic Hydrocarbons," 2 vols., Academic Press Inc., New York, 1964.

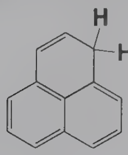
[23] Cruickshank, *Tetrahedron* **17**, 155 (1962).

[24] Kooyman, *Rec. trav. chim.* **66**, 201 (1947).

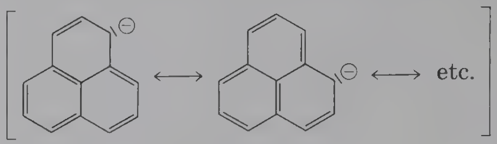
[25] For reviews see Efros, *Russ. Chem. Rev.* **29**, 66–78 (1960); and Badger, *Quart. Rev.* (*London*) **5**, 147–170 (1951).

[26] Wheland, Ref. 1, p. 98.

[27] For a review of phenalenes, see Reid, *Quart. Rev.* (*London*) **19**, 274–302 (1965).

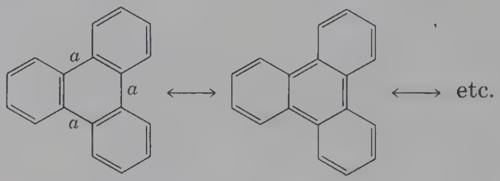


25



26

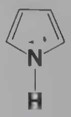
In a fused system there are not six electrons for each ring. In naphthalene, if one ring is to have six, the other must only have four. One way to explain the greater reactivity of the ring system of naphthalene compared to benzene is to regard one of the naphthalene rings as aromatic and the other as a butadiene system.[29] This effect may become extreme as in the case of triphenylene.[30] For this compound, there are eight canonical forms like **27**, in which none of the three bonds marked *a* is a double bond, and only

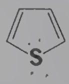


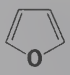
27 **28**

one form, **28**, in which at least one of them is double. So the molecule behaves as if the 18 electrons were distributed so as to give each of the outer rings a sextet, while the middle ring is "empty." Since none of the outer rings need share any electrons with an adjacent ring, they are as stable as benzene; and triphenylene, unlike most fused aromatic hydrocarbons, does not dissolve in concentrated sulfuric acid and has a low reactivity.[31] This phenomenon, whereby in fused systems some rings give up part of their aromaticity to adjacent rings, is called *annellation* and can be demonstrated by ultraviolet spectra[22] as well as by reactivities.

Five-membered Rings. Five-membered rings containing two double bonds can also have an aromatic sextet, if the fifth atom has an unshared pair of electrons. Such is the case in pyrrole, thiophene, and furan, though the latter is not so aromatic as the other two:





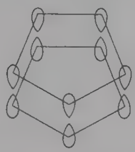


---

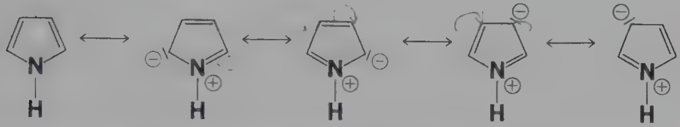
[28] Pettit, *J. Am. Chem. Soc.* **82**, 1972 (1960).
[29] Meredith and Wright, *Can. J. Chem.* **38**, 1177 (1960).
[30] For a review of triphenylenes, see Buess and Lawson, *Chem. Rev.* **60**, 313–330 (1960).
[31] Clar and Zander, *J. Chem. Soc.* **1958**, 1861.

5

Resonance energies for these compounds are, respectively, 21, 29, and 16 kcal/mole.[32] The filled orbital containing the unshared pair overlaps with the adjacent p orbitals to create the aromatic sextet:

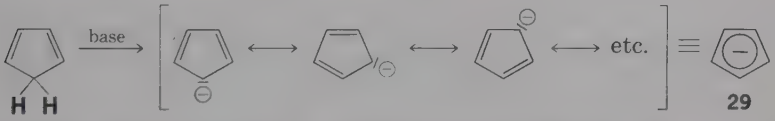


The aromaticity may also be shown by canonical forms; e.g., for pyrrole:



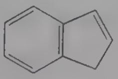
In contrast to the case of pyridine, the unshared pair in pyrrole is needed for the aromatic sextet. This is the reason that pyrrole is so much weaker a base than pyridine.

The fifth atom may be carbon, if it has an unshared pair. Cyclopentadiene has unexpected acidic properties, since on loss of a proton, the resulting carbanion is greatly stabilized by resonance

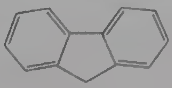


29

although it is quite reactive. The ion is usually represented as in **29**. Resonance in this ion is greater than in pyrrole, thiophene, or furan, since all five forms are equivalent. The calculated resonance energy for **29** is 42 kcal/mole.[33] That all five carbons are equivalent has been demonstrated by labeling the starting compound with ^{14}C and finding all positions equally labeled when cyclopentadiene was regenerated.[34] Indene (**30**) and fluorene (**31**) are also acidic, but less so than cyclopentadiene, since annellation causes the electrons to be less available to the five-membered ring.



30



31

Five-membered aromatic rings are also found in other types of compounds: fulvenes, ylides, and metallocenes. In *fulvenes*[35] (**32**) the exocyclic double bond is greatly polarized in the direction of the ring. These compounds have large dipole moments and react with $LiAlH_4$, which ordinarily does not reduce carbon-carbon double bonds but does so here because of the polarity.

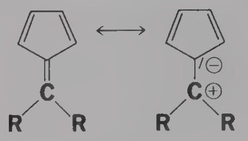
---

[32] Wheland, Ref. 1, p. 99.

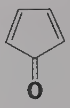
[33] Roberts, Streitwieser, and Regan, *J. Am. Chem. Soc.* **74**, 4579 (1952).

[34] Tkachuk and Lee, *Can. J. Chem.* **37**, 1644 (1959).

[35] For reviews, see Day, *Chem. Rev.* **53**, 167–190 (1953); and Hafner, Häfner, König, Kreuder, Ploss, Schulz, Sturm, and Vöpel, *Angew. Chem. Intern. Ed. Engl.* **2**, 123–134 (1963).



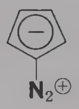
32



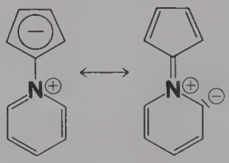
33

Also, cis-trans isomerism is not found in most fulvenes, since the exocyclic bond has a high degree of single-bond character. The ring attracts the electrons so as to have a sextet. In cyclopentadienone (**33**) the oxygen, because of its electronegativity, attracts the electrons from the other side, and this compound is unknown, though some of its derivatives have been prepared.[36]

Ylides are compounds in which two adjacent atoms bear opposite formal charges but the negative atom cannot donate its unshared pair to the bond between them, since the positive atom already has a filled octet. Several types of ylides are known (see especially reaction **6-45**, p. 702), but the ones that concern us here are the cyclopentadienylides. A number of these have been prepared, of which **34** and **35** are examples. **35** is further stabilized by the resonance shown. In these compounds, the cyclopentadiene ring has only four hydrogens, the nitrogen replacing the fifth. The electrons of the C—N bond may be regarded as having come from the nitrogen. Aromatic substitutions have been successfully carried out on **34**.[37]

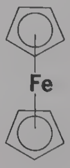


34



35

Metallocenes (also called *sandwich compounds*) are compounds in which two cyclopentadienylide rings form a sandwich around a metallic ion. The most well known of these is ferrocene (**36**), although others have been pre-



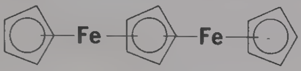
36

---

[36] For a review of cyclopentadienone derivatives and of attempts to prepare the parent compound, see Ogliaruso, Romanelli, and Becker, *Chem. Rev.* **65**, 261–367 (1965).

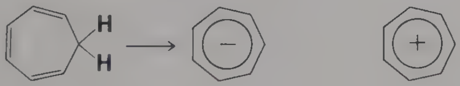
[37] Cram and Partos, *J. Am. Chem. Soc.* **85**, 1273 (1963).

pared with Co, Ni, Cr, Ti, V, and many other metals.[38] Ferrocene is quite stable, subliming above 100°, and is unchanged at 400°. The two rings rotate freely, though the most stable position is a staggered one, in which the rings are not flush. Many aromatic substitutions have been carried out on metallocenes.[39] Compounds of type **37** have been found to arise in mass spectra of ferrocene and have been called "triple-decker sandwiches."[40]

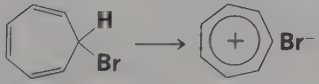


37

Seven-membered Rings.[41] Cycloheptatriene (**38**) is much less acidic than cyclopentadiene. This would be hard to explain without the aromatic-sextet theory, since, on the basis of resonance forms or a simple consideration of orbital overlaps, **39** should be as stable as the cyclopentadienyl anion (**29**). While **39** has been prepared in solution,[42] it is apparently less stable than **29**, and far less stable than **40**, in which **38** has lost not a proton, but a hydride ion. The six double-bond electrons of **40** overlap with the empty orbital on the seventh carbon, and there is a sextet of electrons covering seven carbon atoms. **40**, known as the *tropylium ion,* is quite stable. Tropylium bromide, which could be completely covalent if the electrons of the bromine were sufficiently attracted to the ring, is actually an ionic compound:[43]



38 **39** **40**



Another indication of the stability of **40** is that it is found when toluene is subjected to mass spectroscopy;[44] that is, the $C_6H_5CH_2^+$ ion rearranges to

---

[38] For reviews on metallocenes, see Rausch, *Can. J. Chem.* **41**, 1289–1314 (1963); Fischer and Fritz, *Advan. Inorg. Chem. Radiochem.* **1**, 55–115 (1959); Wilkinson and Cotton, *Progr. Inorg. Chem.* **1**, 1–124 (1959); Pauson, *Quart. Rev. (London)* **9**, 391–414 (1955); Little, *Surv. Progr. Chem.* **1**, 133-210 (1963); and Nesmeyanov, *Bull. Soc. chim. France* **1965**, 1229–1239.

[39] For a review on aromatic substitution on ferrocenes, see Plesske, *Angew. Chem. Intern. Ed. Engl.* **1**, 312–327, 394–399 (1962).

[40] Schumacher and Taubenest, *Helv. Chim. Acta* **47**, 1525 (1964).

[41] For reviews, see Doering and Krauch, *Angew. Chem.* **68**, 661–667 (1956); Cook and Loudon, *Quart. Rev. (London)* **5**, 99–130 (1951); Nozoe, *Progr. Org. Chem.* **5**, 132–163 (1961); Pauson, *Chem. Rev.* **55**, 9–136 (1955); and Doering, in "Theoretical Organic Chemistry, The Kekulé Symposium," pp. 35–48, Butterworth Scientific Publications, London, 1959.

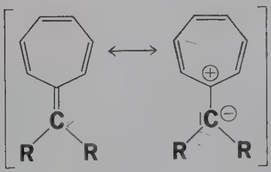
[42] Dauben and Rifi, *J. Am. Chem. Soc.* **85**, 3041 (1963); also see Breslow and Chang, *J. Am. Chem. Soc.* **87**, 2200 (1965).

[43] Doering and Knox, *J. Am. Chem. Soc.* **76**, 3203 (1954).

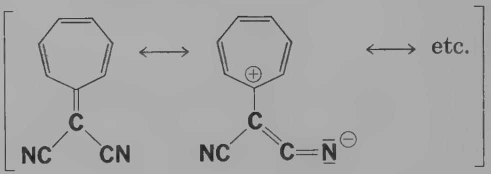
[44] Meyerson, McCollum, and Rylander, *J. Am. Chem. Soc.* **83**, 1401 (1961).

40. Just as with **29**, the equivalence of the carbons in **40** has been demonstrated by isotopic labeling.[45]

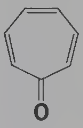
Other types of seven-membered aromatic compounds also illustrate the importance of the sextet. *Heptafulvenes* (**41**) would be expected to have the exocyclic double-bond electrons polarized *away* from the ring. The simplest heptafulvene (R=H) has been prepared,[46] but not isolated, since it is stable only in dilute solution. However, electron-withdrawing groups such as CN would stabilize the negative charge, and **42** is a more stable compound,[47] with a very large dipole moment (7.49 D). In contrast to cyclopentadienone (**33**), cycloheptatrienone, called *tropone* (**43**), is predicted by the sextet theory to be stable, since the seven-membered ring *donates* electrons to the electronegative oxygen, while the five-membered ring requires them. The fact that tropones are stable (and indeed tropolone (**44**) and its derivatives are found in nature), while cyclopentadienones are not, lends strong support to the sextet theory.[48] Although the tropylium ion cannot undergo aromatic substitution, because this requires a positive attacking species, tropolones readily do.



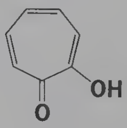
41



42

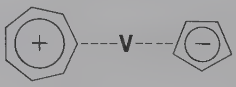


43



44

Metallocenes containing tropylium ions have been prepared, e.g.:[49]



Other Systems Containing Aromatic Sextets. Simple resonance theory predicts that pentalene (**45**), azulene (**46**), and heptalene (**47**) should be aromatic, although no nonionic canonical form can have a double bond at the ring junction. Molecular-orbital calculations show that azulene should be stable but not the other two, and this is borne out by experiment. Heptalene has been prepared[50] but reacts readily with oxygen, acids, and bromine and is easily hydrogenated. Pentalene has not been prepared, but the hexaphenyl derivative is known.[51] This compound is air-sensitive in solution. Many other attempts at preparing these two systems have failed. One approach to hard-to-make aromatic systems involves preparation of ketones which can tautomerize to the desired phenolic systems. In such an attempt to produce a pentalene, **48** was prepared.[52] However, it did not tautomerize to the enol form (see p. 59):

---

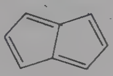
[45] Vol'pin, Kursanov, Shemyakin, Maimind, and Neiman, *J. Gen. Chem. USSR* **29**, 3667 (1959).

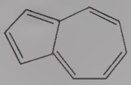
[46] Doering and Wiley, *Tetrahedron* **11**, 183 (1960).

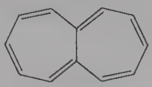
[47] Yamakawa, Watanabe, Mukai, Nozoe, and Kubo, *J. Am. Chem. Soc.* **82**, 5665 (1960); Nozoe, Mukai, Osaka, and Shishido, *Bull. Chem. Soc. Japan* **34**, 1384 (1961).

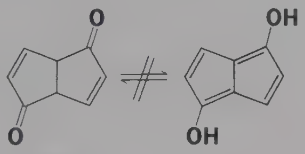
[48] For a review of tropones and tropolones, see Pauson, *Chem. Rev.* **55**, 9–136 (1955).

[49] King and Stone, *J. Am. Chem. Soc.* **81**, 5263 (1959).


45


46

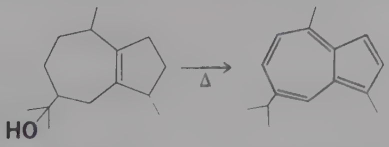

47



48

For pentalene, the only way each ring can have a sextet is for four electrons to be shared by the two rings, which is apparently not a stable situation. In heptalene, each ring can have six electrons, but then the two central carbons must belong to each sextet, and this is not a stable system either.

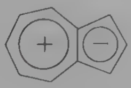
On the other hand, azulene can have six electrons in each ring if they share a pair (as in naphthalene). In sharp contrast to **45** and **47**, azulene is quite stable, and many of its derivatives are known.[53] Many sesquiterpenes, found in nature, are easily converted to azulene derivatives, e.g. (see reaction **9-1**, p. 859),



Guaiol *S-Guaiazulene*

Azulene readily undergoes aromatic substitution.

Azulene may be regarded as a combination of **29** and **40**:



---

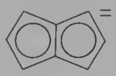
[50] Dauben and Bertelli, *J. Am. Chem. Soc.* **83**, 4659 (1961).

[51] LeGoff, *J. Am. Chem. Soc.* **84**, 3975 (1962).

[52] Baker and McOmie, *Progr. Org. Chem.* **3**, 44–80 (1955), p. 69.

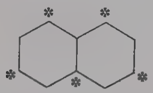
[53] For reviews on azulene, see Reid, Chemical Society Symposia, *Chem. Soc. (London) Spec. Publ.* **12**, 69–83, (1958); Hafner, *Angew. Chem.* **70**, 419–430 (1958); Gordon, *Chem. Rev.* **50**, 127–200 (1952).

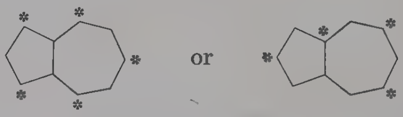
and, indeed, possesses a dipole moment of 1.0 D. Interestingly, if two electrons are added to pentalene to give a dianion, each ring can have a sextet with one pair belonging to both. Such a dianion (**49**) has been prepared,[54] although pentalene itself is not known. It may be concluded that an aromatic system of electrons will be spread over two rings only if 10 electrons, and not 8 or 12, are available for aromaticity.



49

Alternant and Nonalternant Hydrocarbons.[55] Aromatic hydrocarbons may be divided into two types. In alternant hydrocarbons, the conjugated carbon atoms can be divided into two sets, such that no two atoms of the same set are directly linked. For convenience one set may be starred. Naphthalene is an alternant and azulene a nonalternant hydrocarbon:





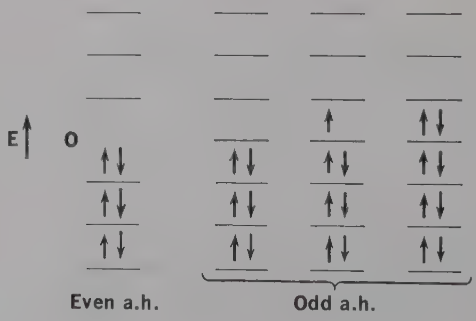
In alternant hydrocarbons, the bonding and antibonding orbitals occur in pairs. That is, for every bonding orbital with an energy $-E$ there is an antibonding one with energy $+E$ (Figure 4). Even-alternant hydrocarbons are those with an even number of conjugated atoms (i.e., an equal number of starred and unstarred atoms). For these hydrocarbons all the bonding

---

[54] Katz, Rosenberger, and O'Hara, *J. Am. Chem. Soc.* **86**, 249 (1964).

[55] For discussions, see Dewar, *Progr. Org. Chem.* **2**, 1–28 (1953); and Longuet-Higgins, in "Theoretical Organic Chemistry. The Kekulé Symposium," pp. 9–19, Butterworth Scientific Publications, London, 1959.

Figure 4. *Energy levels in odd- and even-alternant hydrocarbons (a.h.).*[56] *The arrows represent electrons. The orbitals are shown as having different energies, but some of them may be degenerate.*



[56] Taken from Dewar, Ref. 55, p. 8.

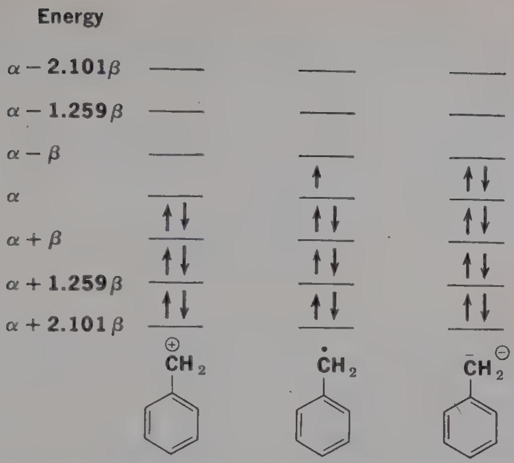
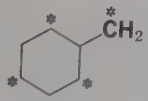


Figure 5. *Energy levels for the benzyl cation, free radical, and carbanion. Since α is the energy of a p orbital (p. 29), the nonbonding orbital has no bonding energy.*

orbitals are filled; the π electrons are uniformly spread over the unsaturated atoms, and there is no dipole moment.

Odd-alternant hydrocarbons (which must be carbonium ions, carbanions, or free radicals) have, in addition to equal and opposite bonding and antibonding orbitals, also a *nonbonding orbital* of zero energy. This follows from the principle that the number of molecular orbitals formed is equal to the number of atomic orbitals which overlap. When an odd number of orbitals overlap, there is an odd number created. Since orbitals of alternant hydrocarbons occur in $-E$ and $+E$ pairs, one orbital can have no partner and must therefore have zero bonding energy. For example, in the benzyl system the cation has an unoccupied nonbonding orbital, the free radical has one electron there, and the carbanion two (Figure 5). This means that all three species have the same bonding energy, since the electrons in the nonbonding orbitals do not contribute, positively or negatively. The charge distribution (or unpaired-electron distribution) over the entire molecule is also the same for the three species and may be calculated by a relatively simple process.[55]

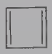


For nonalternant hydrocarbons the energies of the bonding and antibonding orbitals are not equal and opposite, and charge distributions are not the same in cations, anions, and radicals. Calculations are much more difficult but have been carried out.[57]

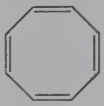
---

[57] Peters, *J. Chem. Soc.* **1958,** 1023, 1028, 1039. For a review, see Zahradnik, *Angew. Chem. Intern. Ed. Engl.* **4,** 1039–1050 (1965).

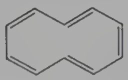
Aromatic Systems with Electron Numbers Other than Six. Ever since the special stability of benzene was recognized, chemists have been thinking about homologous molecules and wondering if this stability would also be associated with rings that are similar but of different sizes, such as cyclobutadiene (**50**), cyclooctatetraene (**51**), cyclodecapentaene[58] (**52**), etc. The general name *annulene* is given to these compounds, with benzene being [6]annulene, and **50** to **52** being called, respectively, [4]-, [8]-, and [10]annulene. By a naive consideration of resonance forms, these annulenes, and higher ones, should be as aromatic as benzene. Yet they proved remarkably elusive. The benzene ring is ubiquitous, being found in thousands of natural products, in coal and petroleum, and being formed by strong treatment of many noncyclic compounds. None of the other annulene ring systems has ever been found in nature, and, except for cyclooctatetraene, their synthesis is not simple. Many annulenes have still not been prepared. Obviously, there is something special about the number six in a cyclic system of electrons.



50

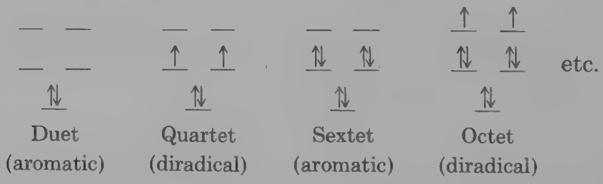


51



52

Hückel's rule, based on molecular-orbital calculations, predicts that electron rings will constitute an aromatic system only if they contain a number of the form $4n + 2$, where n is any positive integer, including zero. The rule predicts that rings of 2, 6, 10, 14, etc., electrons would be aromatic, while rings of 4, 8, 12, etc., would not be. This is actually a consequence of Hund's rule (p. 7). The first pair of electrons in an annulene goes into the π orbital of lowest energy. After that the bonding orbitals are degenerate, occurring in pairs of equal energy:



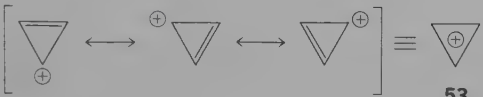
so that when there is a total of four electrons, Hund's rule predicts that two will be in the lowest orbital, but the other two will be unpaired, so that the system will exist as a diradical rather than as two pairs. It is theoretically possible for the four electrons of **50** to pair up in two orbitals, but only if the molecule assumes a rectangular, rather than a square, shape. In this case, of course, the double bonds are essentially separate, and the molecule is still not aromatic. Similar arguments apply to higher systems, though, for very large systems, molecular-orbital theory predicts bond alternation even when there are $4n + 2$ electrons.[59] Calculations show that alternation should begin at $n = 6$, so that the largest aromatic ring should have 22 electrons.[60] In the following sections are discussed systems with various numbers of electrons.

---

[58] The cyclodecapentaene shown here is the cis-trans-cis-cis-trans form. Other stereoisomers are, of course, also possible.

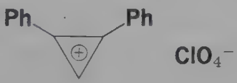
[59] Longuet-Higgins and Salem, *Proc. Roy. Soc.* (*London*) **A251,** 172 (1959), **A257,** 445 (1960).

Systems of Two Electrons.[61] Obviously, there can be no ring of two carbon atoms, though a double bond may be regarded as a degenerate case. However, in analogy to the tropylium ion, a three-membered ring with a double bond and a positive charge on the third atom (the *cyclopropenyl cation*) might be expected to show aromaticity:

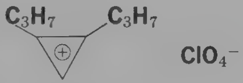


53

The unsubstituted compound has not been made, but **54** and **55** have been prepared and are stable, despite the angles of only 60°.[62] Also, **56, 57,** and

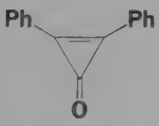


54

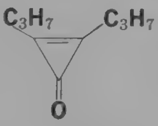


55

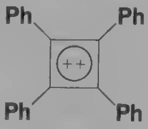
similar cyclopropenones are stable,[63] in accord with the corresponding stability of tropone (**43**). The ring system **53** is nonalternant, and the corresponding radical and anion (which do not have an aromatic duet) have electrons in antibonding orbitals, so that their energies are much higher.



56



57



58

The interesting dication **58** has been prepared,[64] and it too should represent an aromatic system of two electrons.

Systems of Four Electrons. Hückel's rule predicts no aromaticity here, and up to now all the evidence is in accord with this. **59** is an unknown system, and though pentaphenyl and pentachloro derivatives of **60** have been prepared,[65] these ions show at least some diradical character, giving strong electron-paramagnetic-resonance signals (see p. 196). This is in spite of the fact that simple resonance theory predicts no difference between **59** and the cyclopropenyl cation (**53**); and between **60** and the cyclopentadienyl anion (**29**).

---

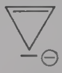
[60] Dewar and Gleicher, *J. Am. Chem. Soc.* **87,** 685 (1965).

[61] For a review, see Krebs, *Angew. Chem. Intern. Ed. Engl.* **4,** 10–22 (1965). For a general discussion, see Vol'pin, Koreshkov, Dulova, and Kursanov, *Tetrahedron* **18,** 107 (1962). Also see Carter and Frampton, *Chem. Rev.* **64,** 497–525 (1964), for a review of cyclopropenes, which includes a large amount of material pertinent to this section.

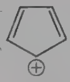
[62] Breslow, Höver, and Chang, *J. Am. Chem. Soc.* **84,** 3168 (1962).

[63] Breslow, Eicher, Krebs, Peterson, and Posner, *J. Am. Chem. Soc.* **87,** 1320 (1965); Breslow, Altman, Krebs, Mohacsi, Murata, Peterson, and Posner, *J. Am. Chem. Soc.* **87,** 1326 (1965); Kursanov, Vol'pin, and Koreshkov, *J. Gen. Chem. USSR* **30,** 2855 (1960); Breslow and Altman, *J. Am. Chem. Soc.* **88,** 504 (1966). For the unsubstituted cyclopropenone, see Breslow and Ryan, *J. Am. Chem. Soc.* **89,** 3073 (1967).

[64] Freedman and Young, *J. Am. Chem. Soc.* **86,** 734 (1964).



59

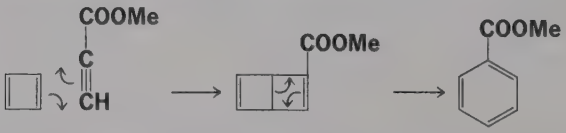


60

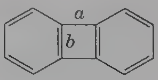
However, the most convincing evidence that four electrons cannot constitute an aromatic system comes from the long history of attempts to prepare cyclobutadiene (**50**) or its simple derivatives.[66] Up to this time the only

50

reported successful attempt to prepare this elusive compound was that of Pettit and coworkers,[67] who treated a metallic complex of cyclobutadiene (see below) with ceric ammonium nitrate at 0° and condensed the resulting gas in a trap cooled with liquid nitrogen. The liquid thus obtained was assumed to be cyclobutadiene. When methyl propiolate was added to it, it gave small amounts of methyl benzoate, which would be expected to form in this manner (see reactions **5-35**, p. 636, and **8-26**, p. 834):



The extreme reactivity of cyclobutadiene and its simple derivatives is not merely caused by steric strain, since the strain should be less than that in cyclopropene, which is a known compound. Derivatives in which the cyclobutadiene system is fused to aromatic rings have been prepared, the most important of which is biphenylene:



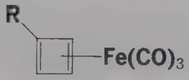
---

[65] Breslow, Chang, and Yager, *J. Am. Chem. Soc.* **85**, 2033 (1963); Volz, *Tetrahedron Letters* **1964**, 1899; Breslow, Hill, and Wasserman, *J. Am. Chem. Soc.* **86**, 5349 (1964); Breslow, Chang, Hill, and Wasserman, *J. Am. Chem. Soc.* **89**, 1112 (1967).

[66] For reviews of attempts to prepare cyclobutadiene and its derivatives, see Criegee, *Angew. Chem. Intern. Ed. Engl.* **1**, 519–527 (1962); *Bull Soc. chim. France* **1965**, 1–6.

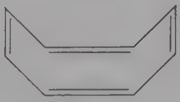
[67] Watts, Fitzpatrick, and Pettit, *J. Am. Chem. Soc.* **87**, 3253 (1965), **88**, 623 (1966). See also Cookson and Jones, *J. Chem. Soc.* **1965**, 1881.

However, annellation (p. 40) can result in an "empty" central ring here, and all the evidence is that this is the case. Thus the bond lengths[68] are *a*, 1.52 Å, and *b*, 1.38 Å. The unfused cyclobutadiene system is stable in complexes with metals[69] (see Chapter 3), but in these cases electron density is withdrawn from the ring by the metal and there is no aromatic quartet. In fact, these cyclobutadiene-metal complexes may be looked upon as systems containing an aromatic duet. Thus, the ring is square planar,[70] the compounds undergo aromatic substitution,[71] and nuclear-magnetic-resonance spectra of monosubstituted derivatives show that the C-2 and C-4 protons are equivalent.[71]



There is evidence that the four electrons of cyclobutadiene exist as two pairs (implying a rectangular shape) rather than as one pair and two unpaired electrons (a diradical). Pettit and coworkers found that cyclobutadiene behaved as a diene in the Diels-Alder reaction, and that the reaction was stereospecific.[72] A diradical cyclobutadiene might give the Diels-Alder reaction, but the addition would not be expected to be stereospecific. Cyclobutadiene also acts as a dienophile in this reaction (**5-34,** p. 626).

Systems of Eight Electrons. Although cyclooctatetraene (**51**) proved to be nonaromatic, this is not necessarily evidence for Hückel's rule, though the contrary would have demolished it. An aromatic system requires planarity of all the carbons, and **51** is not planar, but tub-shaped:[73]



51

The reason for the lack of planarity is that a regular octagon has angles of 135°, while sp^2 angles are most stable at 120°. To avoid the strain, the molecule assumes a nonplanar shape, in which orbital overlap is greatly diminished. Single- and double-bond distances in **51** are, respectively, 1.46 and 1.33 Å, which is just what is expected for a nonaromatic compound.[73] Also the reactivity is what would be expected for a nonaromatic conjugated system. Complexes of cyclooctatetraene with metals are also nonplanar.[74]

---

[68] Mak and Trotter, *J. Chem. Soc.* **1962,** 1.

[69] For example, see Blomquist and Maitlis, *J. Am. Chem. Soc.* **84,** 2329 (1962); Freedman, *J. Am. Chem. Soc.* **83,** 2194, 2195 (1961); Emerson, Watts, and Pettit, *J. Am. Chem. Soc.* **87,** 131 (1965). For a review, see Maitlis, *Advan. Organometal. Chem.* **4,** 95–143 (1966).

[70] Dodge and Schomaker, *Nature* **186,** 798 (1960).

[71] Fitzpatrick, Watts, Emerson, and Pettit, *J. Am. Chem. Soc.* **87,** 3255 (1965).

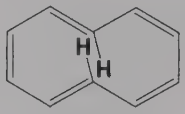
[72] Watts, Fitzpatrick, and Pettit, *J. Am. Chem. Soc.* **88,** 623 (1966).

[73] Bastiansen, Hedberg, and Hedberg, *J. Chem. Phys.* **27,** 1311 (1957).

[74] Dickens and Lipscomb, *J. Chem. Phys.* **37,** 2084 (1962).

The cycloheptatrienyl carbanion (**39**) also has eight electrons, but does not behave as an aromatic system.[41] However, the heptaphenyl derivative of this anion is not a diradical.[75]

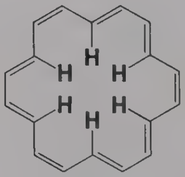
Systems of Ten Electrons and More. Annulenes larger than eight with all cis double bonds have, as does **51**, angles too large for planarity. With rings this large, however, trans double bonds are possible, and configurations can be drawn in which all the angles are 120° and the molecule is planar (for example, **52**). However, Mislow has pointed out that the hydrogens in the 1 and 6 positions of [10]annulene:



52

should interfere with each other and force the molecule out of planarity.[76] According to Mislow, this type of interference is also present in larger systems, up to about [30]annulene, since with trans double bonds there are always hydrogens projecting inside the ring. In recent years a number of large annulenes have been prepared,[77] and their properties bear out both Hückel's rule and, to a certain extent, Mislow's analysis.

One test of aromaticity is the ability to sustain a ring current, and nuclear magnetic resonance has been used to demonstrate which of these annulenes is aromatic. [18]Annulene (**61**) sustains a ring current[78] (see p. 193). X-ray crystallography showed that it was planar, or nearly so, showing that the interference predicted by Mislow is not important in annulenes as large as 18-membered. **61** was reasonably stable, being distillable at reduced pressure, but aromatic substitution attempts failed, and it decomposed slowly on standing.[79] The resonance energy of **61**, calculated from its heat of combus-



61

---

[75] Breslow and Chang, *J. Am. Chem. Soc.* **87**, 2200 (1965).

[76] Mislow, *J. Chem. Phys.* **20**, 1489 (1952).

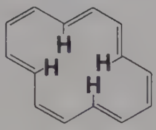
[77] For reviews of annulenes with more than eight carbon atoms, see Sondheimer, *Pure Appl. Chem.* **7**, 363–388 (1963); and Sladkov and Kudryavtsev, *Russ. Chem. Rev.* **32**, 229–243 (1963), pp. 238–240.

[78] Jackman, Sondheimer, Amiel, Ben-Efraim, Gaoni, Wolovsky, and Bothner-By, *J. Am. Chem. Soc.* **84**, 4307 (1962).

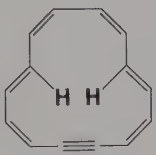
[79] Sondheimer and Wolovsky, *Tetrahedron Letters* **1959**, No. 3, 3.

tion, was found to be about 100 kcal/mole.[80] These results emphasize the differences among the definitions of aromaticity discussed on page 37: that is, **61** sustains a ring current and is greatly stabilized by resonance but is not very stable chemically and does not undergo aromatic substitution.

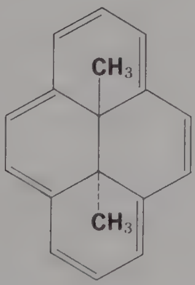
Another annulene expected to be aromatic is [14]annulene (**62**). Although **62** sustains a ring current,[81] it is completely destroyed by light and air in one day. Interference is apparently present here, and x-ray analysis showed that the molecule is not planar.[82] **62** also could not be nitrated or sulfonated, again emphasizing the differences among the definitions of aromaticity. However, the introduction of a triple bond into the [14]annulene ring (**63**) removes two of the interfering hydrogens and allows the molecule to be planar. **63** sustains a ring current and can be nitrated and sulfonated.[83] The extra two electrons of the triple bond do not form part of the aromatic system but simply exist as a localized π bond. Another way of avoiding hydrogen interference is by bridging of the inner valences. Thus *trans*-15,16-dimethyldihydropyrene:



62



63



is a [14]annulene which sustains a ring current and undergoes bromination, nitration, and Friedel-Crafts substitution.[83a]

For Hückel's rule to be correct, [16]- and [24]annulenes would have to be nonaromatic. These molecules do not sustain a ring current,[84] though the larger at least should be planar. Further evidence for Hückel's rule is that trisdehydro[18]annulene (with three triple bonds) is aromatic, but tetrakisdehydro[24]annulene (with four triple bonds), which would be expected to be planar even if [24]annulene were not, is not aromatic.[78]

---

[80] Beezer, Mortimer, Springall, Sondheimer, and Wolovsky, *J. Chem. Soc.* **1965**, 216.

[81] Gaoni, Melera, Sondheimer, and Wolovsky, *Proc. Chem. Soc.* **1964**, 397.

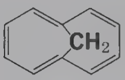
[82] Bregman, *Nature* **194**, 679 (1962).

[83] Gaoni and Sondheimer, *J. Am. Chem. Soc.* **86**, 521 (1964).

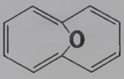
[83a] Boekelheide and Phillips, *J. Am. Chem. Soc.* **89**, 1695 (1967); Phillips, Molyneux, Sturm, and Boekelheide, *J. Am. Chem. Soc.* **89**, 1704 (1967); Boekelheide and Miyasaka, *J. Am. Chem. Soc.* **89**, 1709 (1967).

[84] Ref. 79; Sondheimer, *Pure Appl. Chem.* **7**, 363–388 (1963), pp. 371, 376; Schröder and Oth, *Tetrahedron Letters* **1966**, 4083.

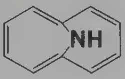
Although [12]annulene is yet unknown, a bisdehydro[12]annulene and a trisdehydro[12]annulene are known and do not sustain ring currents.[85] [10]Annulene has been prepared at −190° but is unstable,[85a] apparently because of the hydrogen interference predicted by Mislow. This is supported by the fact that, as in the case of [14]annulene, stable derivatives are known in which hydrogen interference is avoided by a bridging of the two central valences. Thus, 1,6-methanocyclodecapentaene (**64**),[86] and its oxygen and nitrogen analogs, **65**[87] and **66**,[88] have been prepared and are stable compounds which sustain ring currents and undergo aromatic substitutions. **67**[89] and **68**,[90] which are also 10-electron aromatic systems, have also been prepared.



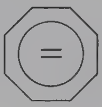
64



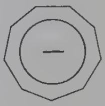
65



66



67



68

Hückel's rule thus appears to be correct, at least up to about 20-membered systems. The situation for larger annulenes needs further study, though the fact that [30]annulene does not appear to be aromatic[91] lends support to the conclusion that aromaticity ends with a system of 22 electrons.[60]

Other Aromatic Compounds. We shall briefly mention three other types of aromatic compounds. *Mesoionic compounds* cannot be satisfactorily repre-

[85] Wolovsky and Sondheimer, *J. Am. Chem. Soc.* **87**, 5720 (1965); Untch and Wysocki, *J. Am. Chem. Soc.* **88**, 2608 (1966); Sondheimer, Wolovsky, Garratt, and Calder, *J. Am. Chem. Soc.* **88**, 2610 (1966).

[85a] van Tamelen and Burkoth, *J. Am. Chem. Soc.* **89**, 151 (1967).

[86] Vogel and Roth, *Angew. Chem. Intern. Ed. Engl.* **3**, 228 (1964); Vogel and Böll, *Angew. Chem. Intern. Ed. Engl.* **3**, 642 (1964); Vogel, Böll, and Biskup, *Tetrahedron Letters* **1966**, 1569. The crystal structure of the 2-carboxylic acid derivative of **64** has been determined by Dobler and Dunitz, *Helv. Chim. Acta* **48**, 1429 (1965). The perimeter is nonplanar, but the bond distances are in the range 1.38 to 1.42 Å.

[87] Sondheimer and Shani, *J. Am. Chem. Soc.* **84**, 3168 (1964); Vogel, Biskup, Pretzer, and Böll, *Angew. Chem. Intern. Ed. Engl.* **3**, 642 (1964).

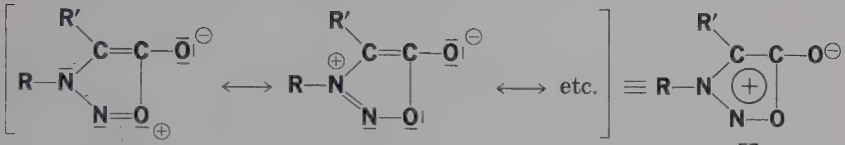
[88] Vogel, Pretzer, and Böll, *Tetrahedron Letters* **1965**, 3613. Also see the second paper of Ref. 87.

[89] Katz, *J. Am. Chem. Soc.* **82**, 3784, 3785 (1960); also see Katz, Yoshida, and Siew, *J. Am. Chem. Soc.* **87**, 4516 (1965).

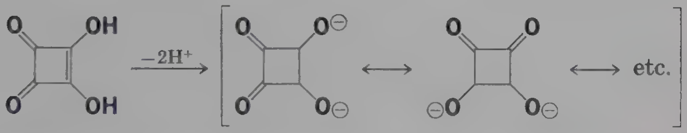
[90] Katz and Garratt, *J. Am. Chem. Soc.* **86**, 5194 (1964); LaLancette and Benson, *J. Am. Chem. Soc.* **87**, 1941 (1965); Simmons, Chesnut, and LaLancette, *J. Am. Chem. Soc.* **87**, 982 (1965).

[91] Sondheimer and Gaoni, *J. Am. Chem. Soc.* **84**, 3520 (1962).

sented by Lewis forms not involving charge separation. *Sydnones*[92] (**69**) are stable aromatic compounds, which undergo aromatic substitution when R′ is hydrogen.[93] Analogous mesoionic compounds are also known.[94]

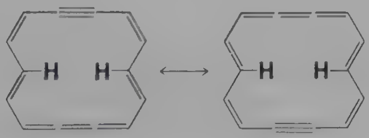

69

Another type of aromatic compound is the dianion of squaric acid:[95]



The stability of this system is illustrated by the fact that the pK_1 of squaric acid is about 1, and the pK_2 about 2, which means that even the second proton is given up much more readily than is the proton of acetic acid, for example. The analogous five- and six-membered ring compounds are also known.

Finally, we may mention 1,8-bisdehydro[14]annulene which has an aromatic system of 14 electrons, is planar, sustains a ring current,[96] and can be successfully nitrated and sulfonated.[83] What makes it interesting is that no Lewis structure can be drawn which does not contain a 1,2,3-triene (cumulene) system.



Free Valence. On page 28 the concept of bond order was discussed. A closely related concept is that of free valence.[97] In the valence-bond method the free valence at a carbon is determined by adding the weights of all the structures in which a Dewar bond ends at that carbon. Free valences at various aromatic positions are shown:

---

[92] For reviews, see Noël, *Bull. Soc. chim. France,* **1964,** 173–177; Stewart, *Chem. Rev.* **64,** 129–147 (1964); Baker and Ollis, *Quart. Rev. (London)* **11,** 15–29 (1957).

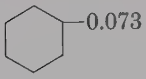
[93] For example, see Tien and Hunsberger, *J. Am. Chem. Soc.* **83,** 178 (1961); and Yashunskii, Vasil'eva, and Sheinker, *J. Gen. Chem. USSR* **29,** 2680 (1959).

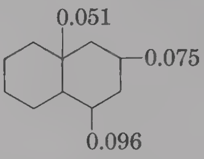
[94] Lawson and Miles, *J. Chem. Soc.* **1959,** 2865.

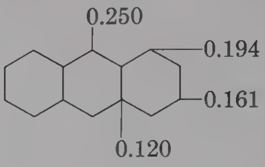
[95] West and Powell, *J. Am. Chem. Soc.* **85,** 2577 (1963); West, Niu, and Ito, *J. Am. Chem. Soc.* **85,** 2580 (1963). For a review, see Maahs and Hegenberg, *Angew. Chem. Intern. Ed. Engl.* **5,** 888–893 (1966).

[96] Sondheimer, Gaoni, Jackman, Bailey, and Mason, *J. Am. Chem. Soc.* **84,** 4595 (1962); Bailey and Mason, *Proc. Chem. Soc.* **1963,** 180.

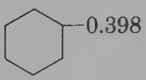
[97] For reviews, see Greenwood and McWeeny, *Advan. Phys. Org. Chem.* **4,** 73–145 (1966); and Pullman and Pullman, *Progr. Org. Chem.* **4,** 31–71 (1958).

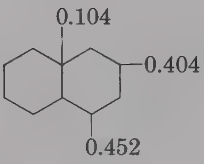


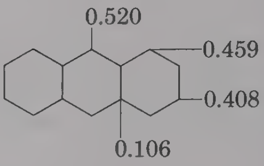




In the molecular-orbital method, free valence is defined as 1.732 minus the sum of the molecular-orbital bond orders to all carbons directly bound.[98] Molecular-orbital free valences for the same compounds are:



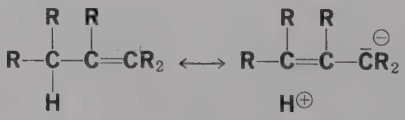




The absolute values of the two methods are not comparable, but the trends are similar in both. The free valence is supposed to be a measure of the ease of attack at a given position. Both methods are in accord with the fact that the 9-position of anthracene is the most reactive, and that it is more reactive than any benzene carbon or any position of naphthalene. For free-valence values for other compounds, see ref. 97.

HYPERCONJUGATION

All of the delocalization so far discussed involves π electrons. Another type, called *hyperconjugation,* involves σ electrons.[99] When a carbon attached to at least one hydrogen is attached to an unsaturated atom, or one with an unshared orbital, canonical forms such as **70** may be drawn.



$$R-\underset{\underset{H}{|}}{\overset{\overset{R}{|}}{C}}-\overset{\overset{R}{|}}{C}=CR_2 \longleftrightarrow R-\overset{\overset{R}{|}}{C}=\overset{\overset{R}{|}}{C}-\overset{\ominus}{\bar{C}}R_2 \quad \underset{}{H^{\oplus}}$$

70

In such canonical forms there is no bond at all between the carbon and hydrogen, and this type of resonance is often called *no-bond resonance.* The hydrogen does not leave (because **70** does not exist but is only a canonical form which contributes to the actual structure of the molecule). The effect of **70** on the actual molecule is that the electrons in the C—H bond are closer to the carbon than they would be if **70** did not contribute at all.

---

[98] 1.732 is chosen as the value for a "completely bonded" carbon. Anything less is the free part of the valence.

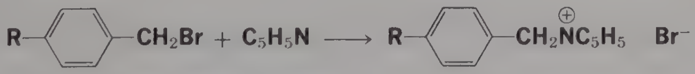
[99] For reviews, see Baker, "Hyperconjugation," Oxford University Press, Fair Lawn, N.J., 1952; Crawford, *Quart. Rev.* (*London*) **3**, 226–244 (1949); symposia in *Tetrahedron* **5**, 107–274 (1959), **17**, 125–289 (1962); and Dewar, "Hyperconjugation," The Ronald Press Company, New York, 1962.

Hyperconjugation in the above case may be regarded as an overlap of the σ orbital of the C—H bond and the π orbital of the C—C bond, analogous to the π-π-orbital overlap previously considered. As might be expected, those who reject the idea of resonance in butadiene (p. 32) believe it even less likely when it involves no-bond structures.

The concept of hyperconjugation arose from the discovery of apparently anomalous electron-release patterns for alkyl groups. By the inductive effect alone, the order of electron release for simple alkyl groups connected to an unsaturated system is *tert*-butyl > isopropyl > ethyl > methyl, and this order is observed in many phenomena. Thus the dipole moments of the alkylbenzenes are, in the gas phase,[100]

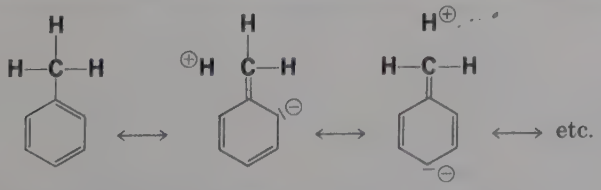
Compound	*Dipole moment, D*
$PhCH_3$	0.37
PhC_2H_5	0.58
$PhCH(CH_3)_2$	0.65
$PhC(CH_3)_3$	0.70

However, Baker and Nathan observed that the rates of reaction with pyridine of *p*-substituted benzyl bromides (see p. 331) were about opposite to that expected from inductive electron release.[101]



R	*k* × *10⁴ at 20°*
CH_3	2.02
C_2H_5	1.81
$CH(CH_3)_2$	1.63
$C(CH_3)_3$	1.65

This came to be called the *Baker-Nathan effect* and has since been found in many processes. Baker and Nathan explained it by considering that hyperconjugative forms contribute to the actual structure of toluene.



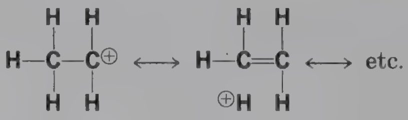
---

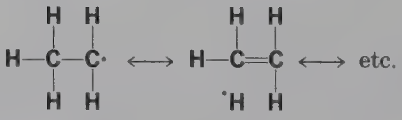
[100] Baker and Groves, *J. Chem. Soc.* **1939,** 1144.

[101] Baker and Nathan, *J. Chem. Soc.* **1935,** 1840, 1844.

For the other alkyl groups, hyperconjugation is diminished, because the number of C—H bonds is diminished, and in *tert*-butyl there are none; hence, with respect to this effect, methyl is the strongest electron donor and *tert*-butyl the weakest. The Baker-Nathan order may be considered to arise when the hyperconjugative resonance effect is greater than the inductive effect.

However, the fact that the Baker-Nathan order is observed in some processes and the inductive order in others has caused considerable controversy as to the reality of hyperconjugation. Over the years, evidence from bond distances, bond energies, spectra, and reactivity has been brought forward to bolster the case for hyperconjugation, and all of these have been attacked as being otherwise caused.[102] Several other explanations have also been brought forward for the Baker-Nathan effect.[103] At present the evidence is against hyperconjugation in the ground states of neutral molecules. However, for carbonium ions and free radicals[104] and for excited states of molecules,[105] there is evidence that hyperconjugation is important. In hyperconjugation in the ground state of neutral molecules, which Muller and Mulliken call *sacrificial hyperconjugation,*[106] the canonical forms involve not only no-bond resonance, but also a charge separation not possessed by the main form. In free radicals and carbonium ions, the canonical forms display no more charge separation than does the main form. Muller and Mulliken call this *isovalent hyperconjugation*:





Even here the main form contributes more to the hybrid than the others.

It is known that the C—F bond distance decreases with the number of fluorines on a carbon.[107] This fact led to the postulation of "reverse" hyper-

---

[102] For attacks see Dewar and Schmeising, *Tetrahedron* **5,** 166 (1959); Dewar, "Hyperconjugation," The Ronald Press Company, New York, 1962; Bent, *Chem. Rev.* **61,** 275–311 (1961), p. 284; Schubert, Murphy, and Robins, *Tetrahedron* **17,** 199 (1962). For support of hyperconjugation, see Mulliken, *Tetrahedron* **6,** 68 (1959); Stock and Himoe, *J. Am. Chem. Soc.* **83,** 1937, 4605 (1961); Ballester and Riera, *Tetrahedron* **20,** 2217 (1964); and Kellogg and Simpson, *J. Am. Chem. Soc.* **87,** 4230 (1965).

[103] Schubert, Craven, Minton, and Murphy, *Tetrahedron* **5,** 194 (1959); Clement and Naghizadeh, *J. Am. Chem. Soc.* **81,** 3154 (1959); Brown, *J. Am. Chem. Soc.* **81,** 3229, 3232 (1959); Schubert and Minton, *J. Am. Chem. Soc.* **82,** 6188 (1960).

[104] Symons, *Tetrahedron* **18,** 333 (1962).

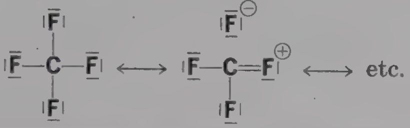
[105] Rao, Goldman, and Balasubramanian, *Can. J. Chem.* **38,** 2508 (1960).

[106] Muller and Mulliken, *J. Am. Chem. Soc.* **80,** 3489 (1958).

[107] From Tables of Interatomic Distances and Configurations in Molecules and Ions, *Chem. Soc. (London), Spec. Publ.* **11** (1959).

Compound	C—F *bond distance, Å*
CF_4	1.32
CHF_3	1.33
CH_2F_2	1.36
CH_3F	1.39

conjugation involving fluorine.[108] According to this hypothesis, the bond shortening is caused by forms like

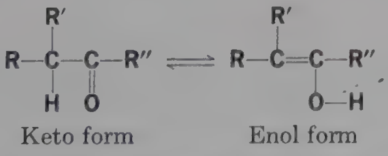


Other evidence, including the fact that the C—F bond becomes stronger with increasing *gem*-fluoro substitution, has been offered in support of this type of resonance, and the same type of picture has been shown in molecular-orbital terms.[109] However, another explanation[110] is that the greatly electronegative fluorine withdraws more *p* than *s* electron density from the carbon, leaving the carbon in CF_4 with more *s* character than in CHF_3, etc. In Chapter 1 it was shown (p. 23) that bonds get shorter with increasing *s* character in the carbon.

TAUTOMERISM

There remains one topic to be discussed in our survey of chemical bonding in organic compounds. For most compounds all the molecules have the same structure, whether or not this structure can be satisfactorily represented by a Lewis formula. But for many other compounds there is a mixture of two or more structurally distinct compounds which are in rapid equilibrium. When this phenomenon, called *tautomerism*,[111] exists, there is a rapid shift, back and forth, among the molecules. In nearly all cases, it is a proton which shifts from one atom of a molecule to another.

Keto-Enol Tautomerism.[112] The most common form of tautomerism is that between a carbonyl compound containing an α hydrogen and its enol form:



---

[108] Brockway, *J. Phys. Chem.* **41**, 185, 747 (1937); Hine, *J. Am. Chem. Soc.* **85**, 3239 (1963).

[109] Williams, *Tetrahedron* **18**, 1477 (1962).

[110] Peters, *J. Chem. Phys.* **38**, 561 (1963).

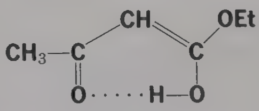
[111] For a review, see Wheland, "Advanced Organic Chemistry," 3d ed., pp. 663–730, John Wiley & Sons, Inc., New York, 1960.

[112] The mechanism for conversion of one tautomer to another is discussed in Chapter 12 (reaction **2-3**, p. 457).

TABLE 1. The enol content of some carbonyl compounds[113]

Compound	*Enol content, %*
Acetone	1.5×10^{-4}
Acetaldehyde	No enol found[114]
CH_3COOEt	No enol found[114]
CH_3COEt	1.2×10^{-1}
Cyclohexanone	1.2
CH_3COCH_2COOEt	8.0
$CH_3COCH_2COCH_3$	76.4
$PhCOCH_2COCH_3$	89.2
$EtOOCCH_2COOEt$	7.7×10^{-3}
$NCCH_2COOEt$	2.5×10^{-1}

In simple cases ($R'' =$ H, alkyl OR, etc.) the equilibrium lies well over to the left. This is the reason that compounds with an OH group and a double bond on the same carbon are usually only hypothetical. When R contains a multiple bond which can be in conjugation with the enolic double bond, a larger amount of enol is present, and it may even be the predominant form (Table 1). As Table 1 shows, esters have much less enolic content than ketones. In molecules like acetoacetic ester, the enol is also stabilized by internal hydrogen bonding, which is unavailable to the keto form:



Frequently, when the enol content is high, both forms may be isolated. The pure keto form of acetoacetic ester melts at −39°, while the enol is a liquid even at −78°. Each can be kept at room temperature for days, if catalysts such as acids or bases are excluded.

The extent of enolization is greatly affected by solvent, concentration, and temperature. Thus, acetoacetic ester has an enol content of 0.4% in water, and 19.8% in toluene.[115] In this case, water reduces the enol concentration by hydrogen bonding with the carbonyl, making this group less available for internal hydrogen bonding.

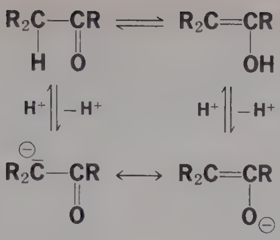
When a strong base is present, both the enol and the keto form can lose a proton. The resulting anion (the *enolate ion*) is the same in both cases. Since **71** and **72** differ only in placement of electrons, *they* are not tautomers, but canonical forms. The true structure of the enolate ion is a hybrid of **71** and **72**, though **72** contributes more, since in this form the negative charge is on the more electronegative atom.

---

[113] Gero, *J. Org. Chem.* **19**, 469, 1960 (1954).

[114] Less than 1 part in 10 million.

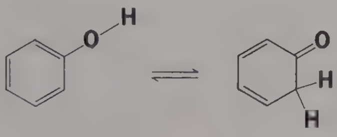
[115] Meyer, *Ann.* **380**, 212 (1911).



71 72

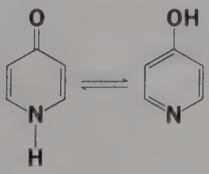
Other Proton-shift Tautomerism. In all such cases, the anion resulting from removal of a proton from either tautomer is the same because of resonance. Some examples are:

1. Phenol-keto tautomerism:[116]

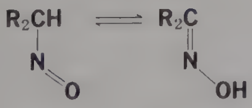


Phenol Cyclohexadienone

This equilibrium lies well over to the side of phenol, since only on that side is there aromaticity. For phenol itself, there is no evidence for the existence of the keto form, though in many heterocyclic compounds, the keto form is actually more stable; for example, 4-pyridone predominates over 4-hydroxypyridine:[117]



2. Nitroso-oxime tautomerism:



$R_2CH-N=O \rightleftharpoons R_2C=N-OH$

Nitroso Oxime

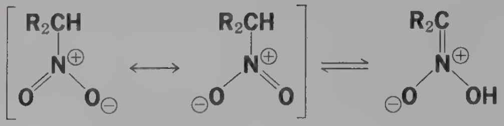
This equilibrium lies far over to the right, and as a rule nitroso compounds are stable only when there is no α hydrogen.

---

[116] For a review, see Thomson, *Quart. Rev. (London)* **10,** 27–43 (1956).

[117] For a discussion, see Katritzky, *Chem. Ind. (London)* **1965,** 331.

3. Aliphatic nitro compounds are in equilibrium with aci forms.



Nitro form Aci form

The nitro form is much more stable than the aci form, in sharp contrast to the parallel case of nitroso-oxime tautomerism, undoubtedly because the nitro form has resonance not found in the nitroso case.

4. Imine-enamine tautomerism:

$$\underset{\text{Imine}}{R_2CH{-}CR{=}NR} \rightleftharpoons \underset{\text{Enamine}}{R_2C{=}CR{-}NHR}$$

Enamines are stable only when there is no hydrogen on the nitrogen ($R_2C{=}CR{-}NR_2$). Otherwise, the imine form predominates.

Ring-chain tautomerism[118] (as in sugars) consists largely of cyclic analogs of the previous examples. There are many other highly specialized cases of proton-shift tautomerism.

Valence Tautomerism. This type of tautomerism is discussed on page 842.

---

[118] For a review, see Jones, *Chem. Rev.* **63**, 461–487 (1963).

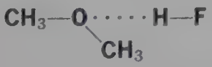
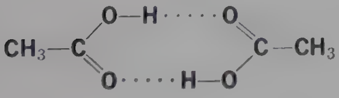
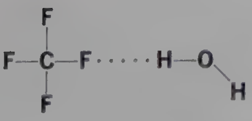
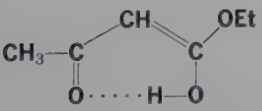
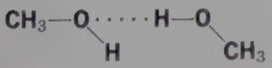
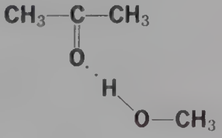
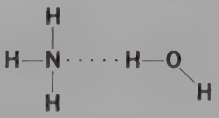
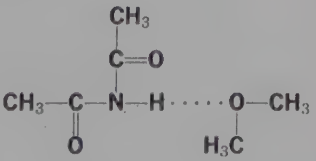
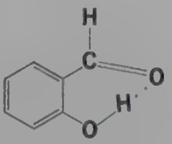
CHAPTER THREE

Bonding Weaker than Covalent

In the first two chapters we have discussed the structure of molecules, each of which is an aggregate of atoms in a distinct three-dimensional arrangement, held together by bonds whose energies are of the order of 50 to 100 kcal/mole. There are also very weak attractive forces *between* molecules, on the order of a few tenths of a kilocalorie per mole. These forces, which are responsible for liquefaction of gases at sufficiently low temperatures, are caused by electrostatic attractions, such as those between dipole and dipole, induced dipole and induced dipole, etc. They are called *van der Waals forces*. The bonding to be discussed in this chapter has energies of the order of 2 to 10 kcal/mole, intermediate between the two extremes, and produces clusters of molecules.

HYDROGEN BONDING

A *hydrogen bond* is a bond between a functional group A—H and an atom or group of atoms B in the same or a different molecule.[1] With exceptions to be noted later, hydrogen bonds are formed only when A is oxygen, nitrogen, or fluorine, and when B is oxygen, nitrogen, or fluorine. The oxygen may be singly or doubly bonded, and the nitrogen singly, doubly, or triply bonded. The bonds are usually represented by dotted lines, as shown in the following examples:

---

[1] For a treatise, see Pimentel and McClellan, "The Hydrogen Bond," W. H. Freeman and Company, San Francisco, 1960.

Hydrogen bonds can exist in the solid and liquid phases, and in solution. Even in the gas phase, compounds which form particularly strong hydrogen bonds may still be associated. Acetic acid, for example, exists in the gas phase as dimers, as shown above, except at very low pressures.[2] In solution and in the liquid phase, hydrogen bonds rapidly form and break. The mean lifetime of the $NH_3 \cdots\cdots H_2O$ bond is 2×10^{-12} sec.[3] Except for the $FH \cdots\cdots F^-$ bond, which has an energy of about 40 kcal/mole, the strongest hydrogen bonds are the $FH \cdots\cdots F$ bond and the bonds connecting one carboxylic acid with another. The energies of these bonds are in the range of 6 to 8 kcal/mole (for carboxylic acids, this refers to the energy of each bond). Other $OH \cdots\cdots O$ bonds and $NH \cdots\cdots N$ bonds have energies of 3 to 6 kcal/mole. To a first approximation, the strength of hydrogen bonds increases with increasing acidity of A—H and basicity of B,[4] but the parallel is far from exact.

The geometry of hydrogen bonds is difficult to determine, since hydrogen is not easy to detect in x-ray-diffraction measurements, but what little evidence there is, is consistent with the hydrogen being on the straight line formed by A and B within about 15°, except in some cases of intramolecular hydrogen bonding where the geometry forbids this.[5] It is significant that the vast majority of intramolecular hydrogen bonding occurs where *six-membered rings* (counting the hydrogen as one of the six) can be formed, in which linearity of the hydrogen bond is geometrically favorable, while five-membered rings, where linearity is usually not favored (though it is known), are much rarer. Except for the special case of $FH \cdots\cdots F^-$ bonds (see p. 65), the hydrogen is not equidistant between A and B. For example, in ice the O—H distance is 0.97 Å, while the $H \cdots\cdots O$ distance is 1.79 Å.[6]

Hydrogen bonding has been detected in many ways, including measurements of dipole moments, solubility behavior, freezing-point lowering, and heats of mixing, but the most important ways are by the effect of the hydrogen bond on infrared, Raman, and electronic spectra[7] (see Chapter 6).

Hydrogen bonds are important because of the effects they have on the properties of compounds. Among these effects are:

1. Intermolecular hydrogen bonding raises boiling points and frequently melting points.
2. If hydrogen bonding is possible between solute and solvent, this greatly increases solubility and often results in large or even infinite solubility where none would otherwise be expected. It is interesting to speculate what the effect on humanity would be if ethyl alcohol had the same solubility in water as ethane or ethyl chloride.
3. Hydrogen bonding causes lack of ideality in gas and solution laws.

---

[2] For a review of hydrogen bonding in carboxylic acids, see Allen and Caldin, *Quart. Rev. (London)* **7**, 255–278 (1953).

[3] Emerson, Grunwald, Kaplan, and Kromhout, *J. Am. Chem. Soc.* **82**, 6307 (1960).

[4] Gordon, *J. Org. Chem.* **26**, 738 (1961).

[5] For a review on the stereochemistry of hydrogen bonds, see Hunter, *Progr. Stereochem.* **1**, 223–249 (1954).

[6] Ref. 1, p. 260.

[7] For a discussion of the effect of hydrogen bonding on electronic spectra, see Lees and Burawoy, *Tetrahedron* **19**, 419 (1963).

4. Hydrogen bonding changes the position of bands in all kinds of spectra, including nuclear magnetic resonance.
5. Hydrogen bonding, especially the intramolecular variety, changes many chemical properties. For example, it is responsible for the large amount of enol present in certain tautomeric equilibria (see p. 60). Also, by influencing the conformation of molecules (see Chapter 4), it often plays a significant role in determining reaction rates.

In addition to oxygen, nitrogen, and fluorine, mentioned earlier, there is evidence that weaker hydrogen bonding exists in other systems. Although many searches have been made for hydrogen bonding where A is carbon,[8] only three types of C—H bonds have been found which are acidic enough to form weak hydrogen bonds. These are found in terminal acetylenes, $RC\equiv CH$, chloroform and some other halogenated alkanes, and HCN. Weak hydrogen bonds are formed by compounds containing S—H bonds.[9] There has been much speculation regarding other possibilities for B. There is evidence that Cl can form weak hydrogen bonds (for example, *o*-chlorophenol is known to exhibit intramolecular hydrogen bonding), but the evidence for Br and I is much less convincing.[10] However, the *ions* Cl^-, Br^-, and I^- form hydrogen bonds which are much stronger than those of the covalently bonded atoms.[11] As we have already seen, the $FH\cdots\cdots F^-$ bond is especially strong. In this case the hydrogen is equidistant from the fluorines. A system which seems to form rather strong hydrogen bonds is the isonitrile system $R{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{\bar{C}}$.[12] There is evidence that double and triple bonds and aromatic rings may be the B component of hydrogen bonds,[13] but these bonds are very weak.

Deuterium also forms hydrogen bonds; in some systems these seem to be stronger than the corresponding hydrogen bonds; in others, weaker.[14]

ADDITION COMPOUNDS

When reaction of two compounds results in a product which contains all the mass of the two compounds, the product is called an *addition compound*.[15] Addition compounds are most often formed from the starting materials in a 1:1 molar ratio, but other integral definite ratios are also known; and some addition compounds contain the starting materials in a nonintegral or even an indefinite ratio. There are several kinds of addition compounds. Two of these do not fall within the scope of this chapter, since they do not contain bonds weaker than covalent bonds:

---

[8] For a survey of C—H hydrogen bonding, see Allerhand and Schleyer, *J. Am. Chem. Soc.* **85,** 1715 (1963).

[9] See, for example, Marcus and Miller, *J. Am. Chem. Soc.* **88,** 3719 (1966) and references given therein.

[10] West, Powell, Whatley, Lee, and Schleyer, *J. Am. Chem. Soc.* **84,** 3221 (1962).

[11] Allerhand and Schleyer, *J. Am. Chem. Soc.* **85,** 1233 (1963); McDaniel and Valleé, *Inorg. Chem.* **2,** 996 (1963).

[12] Ferstandig, *J. Am. Chem. Soc.* **84,** 3553 (1962); Allerhand and Schleyer, *J. Am. Chem. Soc.* **85,** 866 (1963).

[13] For example, see West, *J. Am. Chem. Soc.* **81,** 1614 (1959); DePuy and Story, *Tetrahedron Letters* **1959,** No. 6, 20; Basila, Saier, and Cousins, *J. Am. Chem. Soc.* **87,** 1665 (1965); McPhail and Sim, *Chem. Commun.* **1965,** 124.

[14] Dahlgren and Long, *J. Am. Chem. Soc.* **82,** 1303 (1960); Creswell and Allred, *J. Am. Chem. Soc.* **84,** 3966 (1962).

[15] For a general reference, see Wheland, "Advanced Organic Chemistry," 3d ed., pp. 136–183, John Wiley & Sons, Inc., New York, 1960.

1. Regular covalent compounds, such as the product of reaction of ethylene and bromine.
2. Compounds formed by overlap of an orbital containing an unshared pair with an empty orbital, for example, $H_3N—BF_3$ (see Lewis acids and bases, p. 227).

In other addition compounds the molecules of the starting materials remain more or less intact, and weak bonds hold two or more molecules together in a cluster. We can divide these compounds into three broad classes: charge-transfer complexes, inclusion compounds, and catena compounds.

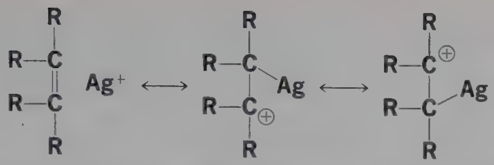
Charge-transfer Complexes.[16] In *charge-transfer complexes,* there is always a donor molecule and an acceptor. The donor may donate an unshared pair (an *n* donor) or a pair of electrons in a π orbital of a double bond or aromatic system (a π donor). One test for the presence of a charge-transfer complex is the electronic spectrum. These complexes always exhibit a spectrum (called a *charge-transfer spectrum*) which is not the same as the sum of the spectra of the two individual molecules. Because the first excited state of the complex is relatively close in energy to the ground state, there is usually a peak in the visible or near-ultraviolet region (see Chapter 6), and charge-transfer complexes are often colored. Many charge-transfer complexes are unstable and exist only in solutions in equilibrium with their components, but others are stable solids. There are several types of acceptor, and we shall classify complexes into three groups, depending on the nature of the acceptor.

1. Complexes in which the acceptor is a metal ion, and the donor an olefin or an aromatic ring (*n* donors do not give charge-transfer complexes with metal ions but form covalent bonds instead).[17] Many metal ions form complexes, which are often stable solids, with olefins, dienes (usually conjugated, but not always), and aromatic rings. The bonding is not simple. Electron density is transferred from the π orbital to the metal, but just how to express the resulting picture is not certain. One way, illustrated for the case of silver ion, is to show the complex as a resonance hybrid:

---

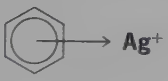
[16] For a monograph, see Andrews and Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, 1964. For reviews, see Andrews, *Chem. Rev.* **54,** 713–776 (1954); and Kosower, *Progr. Phys. Org. Chem.* **3,** 81–163 (1965).

[17] For a general review, see Cais, in Patai, "The Chemistry of Alkenes," pp. 335–385, Interscience Publishers, Inc., New York, 1964. There have been many reviews limited to certain classes of complexes. Among these are: transition metals–olefins and acetylenes, Bennett, *Chem. Rev.* **62,** 611–652 (1962); mercuric ion–olefins, Chatt, *Chem. Rev.* **48,** 7–43 (1951); iron-dienes, Pettit, Emerson, and Mahler, *J. Chem. Educ.* **40,** 175–180 (1963); Pettit and Emerson, *Advan. Organometal. Chem.* **1,** 1–40 (1964); metals-di- and oligoolefins, Fischer and Werner, *Angew. Chem. Intern. Ed. Engl.* **2,** 80–93 (1963); metals-aromatics, Fischer and Fritz, *Angew. Chem.* **73,** 353–363 (1961); metals–allylic compounds, Green and Nagy, *Advan. Organometal. Chem.* **2,** 325–363 (1964); and metals–seven- and eight-membered rings, Bennett, *Advan. Organometal. Chem.* **4,** 353–387 (1966).

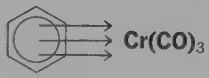


A molecular-orbital picture has been devised,[18] in which there are two bonds between the metal and the olefin. One of these is a σ bond formed by overlap of the filled π orbital of the olefin with the empty 5*s* orbital of the silver ion, and the other is a π bond formed by overlap of a filled 4*d* orbital of the silver and an empty antibonding π orbital of the olefin. In any event the bond is not from the silver to one atom, but to the whole π center.

Among the compounds which form complexes with silver and other metals are benzene (represented as in **1**), cyclooctatetraene, and even cyclobutadiene[19] (see p. 51). When the metal involved has a coordination number greater than 1, more than one donor molecule participates. In many cases, this extra electron density comes from CO groups, which in these complexes are called carbonyl groups. Thus, benzenechromium tricarbonyl (**2**) is a stable compound.[20] Three arrows are shown, since all three aromatic bonding orbitals contribute some electron density to the metal. Metallocenes (p. 42) may be considered a special case of this type of complex, though the bonding in metallocenes is much stronger.



1



2

2. Complexes in which the acceptor is an organic molecule. Picric acid and similar polynitro compounds are the most important of these.[21] Picric acid forms addition compounds with many aromatic hydrocarbons, aromatic amines, aliphatic amines, olefins, and other compounds. These addition compounds are usually solids with definite melting points and are often used as derivatives of the compounds in question. They are called picrates, though they are not salts of picric acid but addition compounds. Unfortunately, salts of picric acid are also called picrates. Not only picric acid but other aromatic nitro compounds and even some aliphatic nitro compounds form similar addition compounds. Similar complexes are formed between phenols and quinones (quinhydrones). Olefins which contain electron-withdrawing substituents also act as acceptor molecules. A particularly strong one is tetracyanoethylene.

The bonding in these cases is more difficult to explain than in the previous case, and indeed no really satisfactory explanation is available.[22] The difficulty is that, although the donor has a pair of electrons to contribute (both n donors and π donors are found here), the acceptor does not have a vacant orbital. Simple attraction of the dipole–induced-dipole type would be too weak to explain the bonding, and is further ruled out by the fact that nitromethane, with about the same dipole moment as nitrobenzene, forms much weaker complexes.

---

[18] Dewar, *Bull. Soc. chim. France* **18,** C79 (1951).

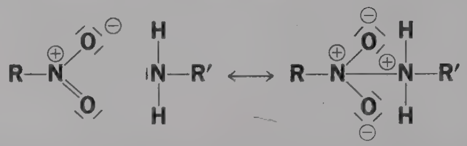
[19] Avram, Marica, and Nenitzescu, *Chem. Ber.* **92,** 1088 (1959); Avram, Fritz, Keller, Mateescu, McOmie, Sheppard, and Nenitzescu, *Tetrahedron* **19,** 187 (1963).

[20] Nicholls and Whiting, *J. Chem. Soc.* **1959,** 551.

[21] For a review, see Parini, *Russ. Chem. Rev.* **31,** 408–417 (1962); also Ref. 16.

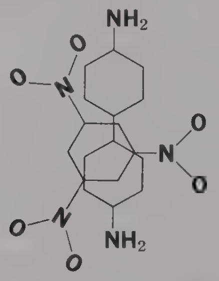
[22] For reviews, see McGlynn, *Chem. Rev.* **58,** 1113–1156 (1958); Briegleb and Czekalla, *Angew. Chem.* **72,** 401–413 (1960); Cauquis and Basselier, *Ann. chim.* (*Paris*) [13] **7,** 745–761 (1962); Murrell, *Quart. Rev.* (*London*) **15,** 191–206 (1961).

One theory is that resonance of the type

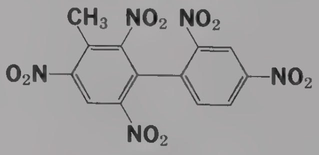


is responsible for attraction between nitro compounds and amines.[23] The amine (an n donor) thus contributes electrons to a partially filled orbital of the nitro group. Presumably, aromatic hydrocarbons and olefins behave similarly, though in these cases π electrons are donated. Another theory, a molecular-orbital one, suggests that electrons from one of the two original molecules can jump into higher vacant orbitals of the other.[24]

One difficulty with these explanations is that they predict that the functional groups should be close to each other, but this is not always so. Crystal structures, determined for a number of addition compounds, have shown that the molecules are stacked in parallel planes. The structure of the complex trinitrobenzene-benzidine



is such that not only are the groups not close to each other, but even the rings do not overlap.[25] The ability to form a plane seems to be important. Thus **3**, in which the two rings cannot be coplanar, did not form a complex with anthracene.[26]



3

---

[23] Mulliken, *J. Am. Chem. Soc.* **74,** 811 (1952).

[24] Dewar and Lepley, *J. Am. Chem. Soc.* **83,** 4560 (1961); Dewar and Rogers, *J. Am. Chem. Soc.* **84,** 395 (1962).

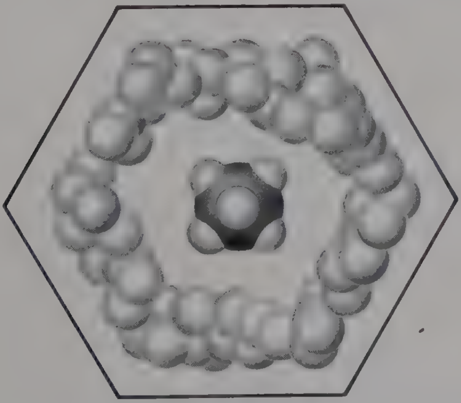
[25] Wallwork, *J. Chem. Soc.* **1961,** 494.

[26] Newman, in Newman (ed.), "Steric Effects in Organic Chemistry," p. 473, John Wiley & Sons, Inc., New York, 1956.

3. Complexes in which the acceptor is I_2, Br_2, or even Cl_2.[27] These molecules accept electrons from both n donors and π donors, presumably by expansion of the outer shell to hold 10 electrons. Such complexes are formed with amines, aromatic hydrocarbons, ketones, etc. This is the reason that iodine is not its normal purple color in solvents such as acetone, ethanol, or benzene. IBr and ICl also form complexes, in which the iodine end of the molecule is the acceptor.[28] Even in these cases the bonding is not simple. The authors of a recent review article state[27] that, despite the presumption about expansion of the octet, "a satisfactory theoretical interpretation of the observed geometry of the atomic arrangements associated with charge-transfer bonding (in these complexes) is still lacking." That there is charge transfer here seems certain, since the iodine-benzene complex has a dipole moment, though iodine and benzene are themselves nonpolar.

Inclusion Compounds. This type of addition compound is quite different from the charge-transfer compounds previously discussed. One of the compounds, called the *host,* forms a crystal lattice in which are spaces large enough for the second compound, called the *guest,* to fit. There is no bonding between the host and the guest except van der Waals forces. There are two main types, depending on the shape of the space. The spaces in *inclusion compounds* are in the shape of long tunnels or channels, while the other type, often called *clathrate,* or *cage, compounds* have spaces which are completely enclosed. In both types the guest molecule must just fit into the space, and potential guests which are too large or too small will not go into the lattice, so that the addition compound will not form.

The most important host molecule among the inclusion compounds is urea. Ordinary crystalline urea is tetragonal, but when a guest is present, urea crystallizes in a hexagonal lattice, containing the guest in long channels:[29]



The hexagonal type of lattice can form only when a guest molecule is present, showing that van der Waals forces between the host and the guest, while small, are essential to the stability of the structure. The diameter of the channel is about 5 Å, and which molecules can be guests is dependent only on their shapes and sizes and not on any electronic or chemical effects. For example, octane and 1-bromooctane are suitable guests for urea, but 2-bromooctane, 2-methylheptane, and 2-methyloctane are not. Also both dibutyl maleate and dibutyl fumarate are guests; neither diethyl maleate or diethyl fumarate is a guest, but dipropyl fumarate is a guest and dipropyl maleate is not.[30] In these complexes, there is usually no integral molar ratio (though by chance there may be). For example, the octane-urea ratio is 1:6.73.[31]

---

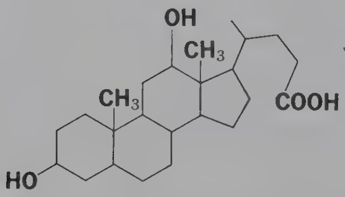
[27] For a review, see Hassel and Rømming, *Quart. Rev.* (*London*) **16,** 1–18 (1962).

[28] Augdahl and Klaeboe, *Acta Chem. Scand.* **16,** 1647, 1655 (1962).

[29] This picture is taken from a paper by Montel, *Bull. Soc. chim. France* **1955,** 1013.

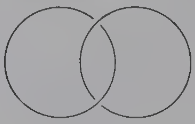
The complexes are solids but are not useful as derivatives, since they melt, with decomposition of the complex, at the melting point of urea. They are useful, however, in separating isomers which would be quite difficult to separate otherwise.

Thiourea also forms inclusion compounds, but with channels of larger diameter, so that *n*-alkanes cannot be guests, but, for example, 2-bromooctane, cyclohexane, and chloroform readily fit. There are a number of other host compounds which form inclusion compounds, the most notable of which is deoxycholic acid:



Clathrate Compounds.[32] The most important host for this type of compound is hydroquinone. Three molecules, held together by hydrogen bonding, make a cage in which fits one molecule of guest. Typical guests are methanol (but not ethanol), SO_2, CO_2, and argon (but not neon). In contrast to the inclusion compounds, the crystal lattices here can exist partially empty. Another host is water. Usually six molecules of water form the cage, and many guest molecules, among them Cl_2 and methyl iodide, can fit. The water clathrates, which are solids, can normally be kept only at low temperatures; at room temperature they decompose.

Catena Compounds. Catena compounds contain two rings which are not bonded to each other but are held together as links in a chain:



Catena compounds are discussed on page 905.

---

[30] Radell, Connolly, and Cosgrove, *J. Org. Chem.* **26**, 2960 (1961).

[31] Redlich, Gable, Dunlop, and Millar, *J. Am. Chem. Soc.* **72**, 4153 (1950).

[32] For reviews, see Child, *Quart. Rev.* (*London*) **18**, 321–346 (1964), and Mandelcorn, *Chem. Rev.* **59**, 827–839 (1959).

CHAPTER FOUR

Stereochemistry

In the previous chapters we have described what is known about electron distribution in molecules. In this chapter we shall discuss the three-dimensional structure of organic compounds.[1] The structure may be such that *stereoisomerism* is possible. Stereoisomers are compounds made up of the same atoms bonded by the same bonds, but having different three-dimensional structures which are not interchangeable. These three-dimensional structures are called *configurations.* There are two kinds of stereoisomerism: *optical isomerism* and *geometrical isomerism,* although as will be seen later, in some cases it is not easy to draw a distinction between them.

OPTICAL ISOMERISM AND OPTICAL ACTIVITY

A material which rotates the plane of polarized light is said to be *optically active.* If a pure compound is optically active, then the molecule is nonsuperimposable on its mirror image. If a molecule is superimposable on its mirror image, then the compound does not rotate the plane of polarized light; it is optically inactive. Although this relationship is empirical, it is absolute. No exceptions are known, and many thousands of cases have been found in accord with it (however, see p. 74). The ultimate criterion, then, for optical activity is nonsuperimposability on the mirror image. This is both a necessary and a sufficient condition. This fact has been used as evidence for the structure determination of many compounds, and historically the tetrahedral nature of carbon was deduced from the hypothesis that the relationship might be true.

If a molecule is nonsuperimposable on its mirror image, then the mirror image must be a different molecule, and in each case of optical activity of a pure compound there are two and only two isomers, called *enantiomers* (sometimes *enantiomorphs*), which differ in structure only in the left- and right-handedness (handedness is also called *chirality*) of their orientations (Figure 1). Enantiomers have identical physical and chemical properties, except in two important respects:

1. They rotate the plane of polarized light in opposite directions, though in equal amounts. The isomer which rotates the plane to the left (counter-

---

[1] For excellent lengthy treatments of this subject, see Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, New York, 1962; Mislow, "Introduction to Stereochemistry," W. A. Benjamin Inc., New York, 1965; Wheland, "Advanced Organic Chemistry," 3d ed., pp. 195–514, John Wiley & Sons, Inc., New York, 1960; and Shriner, Adams, and Marvel, in Gilman, "Advanced Organic Chemistry," vol. 1, 2d ed., pp. 214–488, John Wiley & Sons, Inc., New York, 1943. Although the latter review is not recent, most of it remains quite valid and useful.

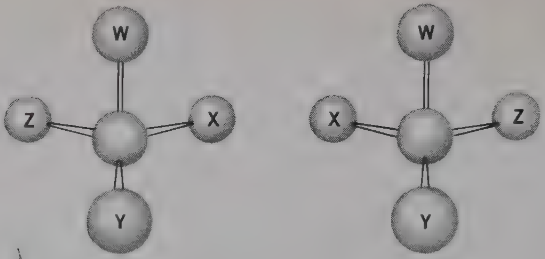


Figure 1. *Enantiomers.*

[illegible]
Convenient
rate

clockwise) is called the *levo* isomer and is designated (−), while the one which rotates the plane to the right (clockwise) is called the *dextro* isomer and is designated (+).

2. They react at different rates with other optically active compounds. These rates may be so close together as to make the distinction practically useless, or they may be so far apart that one enantiomer undergoes the reaction at a convenient rate, while the other does not react at all. It is for this reason that many compounds are biologically active while their enantiomers are not.

In general it may be said that enantiomers have identical properties in a symmetric environment, but in an asymmetric environment their properties may differ. Besides the important differences previously noted, enantiomers may react at different rates with inactive molecules if there is an optically active *catalyst* present; they may have different solubilities in an optically active *solvent;* they may have different indexes of refraction or absorption spectra *when examined with circularly polarized light,* etc. In most cases these differences are too small to be useful and are often too small to be measured.

Although pure compounds are always optically active if they are composed of molecules which are nonsuperimposable on their mirror images, mixtures of equal amounts of enantiomers are optically inactive, since the rotations cancel. Such mixtures are called *racemic mixtures.* Their properties are not always the same as those of the individual enantiomers. Usually the properties in the gaseous or liquid state, or in solution, are the same, since such a mixture is nearly ideal, but properties involving the solid state, such as melting points and solubilities, are often different. Thus racemic tartaric acid has a melting point of 204–6° and a solubility in water at 20° of 206 g/liter; while for the (+) or the (−) enantiomer, the corresponding figures are 170° and 1390. The separation of a racemic mixture into its two optically active components is called *resolution.*

Dependence of Rotation on Conditions of Measurement. The *amount* of rotation (α) is not a constant for a given enantiomer; it depends on the length of the sample vessel, the temperature, the solvent and concentration (for solutions), the pressure (for gases), and the wavelength of light used. Of course, rotations determined for the same compound under the same conditions are identical. The length of the vessel and the concentration or pressure determine the number of molecules in the path of the beam, and α is linear with this. Therefore, a number is defined, called the *specific rotation* ($[\alpha]$), which is, for solutions,

$$[\alpha] = \frac{\alpha}{lc}$$

and, for pure compounds,

$$[\alpha] = \frac{\alpha}{ld}$$

where α is the observed rotation, l is the cell length in decimeters, c is the concentration in grams per milliliter, and d is the density in the same units. The specific rotation is usually given along with the temperature and wavelength, in this manner: $[\alpha]_{546}^{25^\circ}$. These conditions must be duplicated for comparison of rotations, since there is no way to put them into a simple formula. The expression $[\alpha]_\mathrm{D}$ means that the rotation was measured with sodium D light; that is $\lambda = 589$ mμ. The molar rotation $[M]_\lambda^t$ is the specific rotation times the molecular weight, divided by 100.

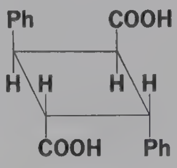
It must be emphasized that, although the value of α changes with conditions, the molecular structure is unchanged. This is true even when the changes in conditions are sufficient to change not only the amount of rotation, but even the direction. Thus one of the enantiomers of aspartic acid, when dissolved in water, has $[\alpha]_\mathrm{D}$ equal to $+4.36^\circ$ at 20° and -1.86° at 90°, though the molecular structure is unchanged. A consequence of cases like this is that there is a temperature at which there is *no* rotation; in this case 75°. Of course, the other enantiomer exhibits opposite behavior. Other cases are known in which the direction of rotation is reversed by changes in wavelength (this is common; see the discussion of optical rotatory dispersion on page 110), solvent, and even concentration.[2] In theory, there should be no change in $[\alpha]$ with concentration, since this is taken into account in the formula, but associations, dissociations, and solute-solvent interactions often cause nonlinear behavior. The change with cell length must be linear, and this fact is used to determine when rotations are greater than 180°. For example, a rotation of 18° might be equally 198° or 378°, etc. Measuring the rotation in a cell one-third the length would give 6° in the first case, 66° in the second, and 126° in the third.

What Kinds of Molecules Display Optical Activity? The ultimate criterion is, of course, nonsuperimposability on the mirror image, but other tests may be used, which are simpler to apply, but which are not always accurate. One such test is the presence of a *plane of symmetry*. A plane of symmetry (also called a *mirror plane*) is one which cuts the molecule into two parts so that each part is the mirror image of the other. *Compounds possessing such a*

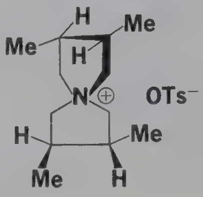
---

[2] For examples, see Shriner, Adams, and Marvel, Ref. 1, pp. 291–301.

plane are always optically inactive, but there are a few cases known in which compounds lack a plane of symmetry and are nevertheless inactive. Such compounds possess a *center of symmetry,* such as in α-truxillic acid (**1**), or an alternating axis of symmetry as in **2**.[3]



1

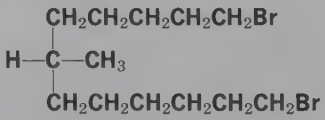


2

A molecule which contains just one *asymmetric carbon atom* (defined as a carbon atom connected to four different groups) is always nonsuperimposable on its mirror image and hence optically active. As seen in Figure 1, such a molecule cannot have a plane of symmetry, whatever the identity of **W**, **X**, **Y**, and **Z**, so long as they are all different. However, the presence of an asymmetric carbon is neither a necessary nor a sufficient condition for optical activity, since optical activity may be present in molecules with no asymmetric atom and since some molecules with two or more asymmetric carbon atoms are superimposable on their mirror images and hence inactive. Examples of such compounds will be discussed subsequently.

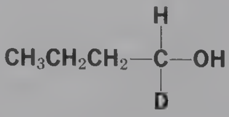
Optically active compounds may be classified into several categories.

1. *Compounds with an asymmetric carbon atom.* If there is only one such atom, the molecule must be optically active. This is so no matter how slight the differences are among the four groups. For example, optical activity is present in



$$\begin{array}{c} CH_2CH_2CH_2CH_2CH_2Br \\ H-\overset{|}{\underset{|}{C}}-CH_3 \\ CH_2CH_2CH_2CH_2CH_2CH_2Br \end{array}$$

Optical activity has been detected even in such cases as 1-butanol-1-*d*, where one group is hydrogen and another deuterium:[4]



$$CH_3CH_2CH_2-\overset{\overset{H}{|}}{\underset{\underset{D}{|}}{C}}-OH$$

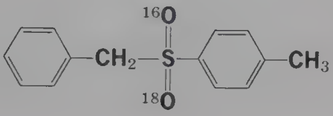
However, the amount of rotation is greatly dependent on the nature of the four groups, in general increasing with increasing differences in polarizabilities among the groups. Alkyl groups have very similar polarizabilities, and the optical activity of 5-ethyl-5-propylundecane was too low to be measurable at any wavelength between 2800 and 5800 Å.[5]

---

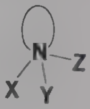
[3] McCasland and Proskow, *J. Am. Chem. Soc.* **77**, 4688 (1955).

[4] Streitwieser and Schaeffer, *J. Am. Chem. Soc.* **78**, 5597 (1956).

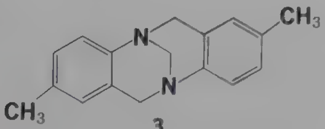
2. *Compounds with other asymmetric atoms.*[6] Any molecule containing an atom which has four bonds pointing to the corners of a tetrahedron will be optically active if the four groups are different. Among atoms in this category are Si, Ge, N (in quaternary salts or N-oxides) and certain metals, such as Cu, Pt, and Pd, which form tetrahedral coordination compounds. In sulfones the sulfur bonds tetrahedrally, but since two of the groups are always oxygen, no optical activity can normally result. However, the preparation[7] of an optically active sulfone in which one oxygen is ^{16}O and the other ^{18}O illustrates the point that slight differences in groups are all that is necessary:



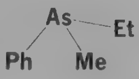
Elements with pyramidal bonding[8] might be expected to give rise to optical activity if the atom is connected to three different groups, since the unshared pair of electrons is analogous to a fourth group, necessarily different from the others:



However, it has never proved possible to demonstrate optical activity in suitably substituted open-chain amines. This is due to the *umbrella effect,* in which the nitrogen with the unshared pair rapidly oscillates from one side of the XYZ plane to the other, thus converting the molecule to its enantiomer millions of times a second. For ammonia there are 2 × 10^{11} inversions every second. In molecules in which the nitrogen is at a bridgehead, the inversion is prevented, and, for example, optically active **3** (Tröger's base) has been prepared.[9] Phosphorus inverts more slowly and arsenic still more slowly.



3



4

---

[5] Wynberg, Hekkert, Houbiers, and Bosch, *J. Am. Chem. Soc.* **87,** 2635 (1965).

[6] For a review of compounds with asymmetric noncarbon atoms, see Sokolov and Reutov, *Russ. Chem. Rev.* **34,** 1–12 (1965).

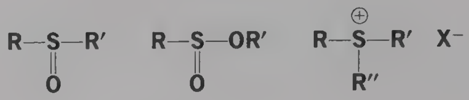
[7] Stirling, *J. Chem. Soc.* **1963,** 5741.

[8] For a review of the stereochemistry of the Group V elements, see Mann, *Progr. Stereochem.* **2,** 196–227 (1958).

[9] Prelog and Wieland, *Helv. Chim. Acta* **27,** 1127 (1944).

Optically active nonbridgehead phosphorus,[10] arsenic, and antimony compounds have been resolved, for example, **4.**[11] Sulfur exhibits pyramidal bonding in sulfoxides, sulfinic esters, and sulfonium salts:

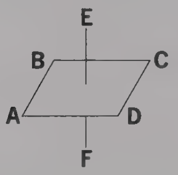
S



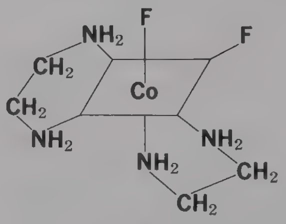
$$R{-}\underset{\underset{O}{\|}}{S}{-}R' \qquad R{-}\underset{\underset{O}{\|}}{S}{-}OR' \qquad R{-}\overset{\oplus}{\underset{\underset{R''}{|}}{S}}{-}R' \quad X^-$$

Examples of each of these have been resolved.[12]

3. *Compounds containing suitably substituted octahedral atoms.* Many metals form coordination compounds with six ligands. These may be nonsuperimposable on their mirror images if the ligands are sufficiently different. No compound with six different groups (**5**) has yet been resolved,[13] though such compounds are theoretically resolvable. Many compounds with bidentate ligands, for example, the *cis*-difluoro-bis(ethylenediamine)cobalt (III) ion (**6**) have been resolved.[13a]



5



6

4. *Restricted rotation giving rise to perpendicular disymmetric planes.* Certain compounds which do not contain asymmetric atoms are nevertheless optically active, because they contain a structure which may be schematically represented as in Figure 2. For these compounds we may draw two perpendicular planes, neither of which can be bisected by a plane of symmetry. If either plane could be so bisected, then the molecule would be superimposable on its mirror image, since such a plane would be a plane of symmetry. These points will be illustrated by examples.

Biphenyls containing four large groups in the ortho positions cannot freely rotate about the central bond, because of steric hindrance. In such com-

---

[10] Horner, *Pure Appl. Chem.* **9**, 225 (1964).

[11] Horner and Fuchs, *Tetrahedron Letters* **1962**, 203.

[12] For discussion, see Shriner, Adams, and Marvel, Ref. 1, pp. 419–423.

[13] Wilkins and Williams, in Lewis and Wilkins, "Modern Coordination Chemistry," pp. 174–228, Interscience Publishers, Inc., New York, 1960. This is a review article on the stereochemistry of coordination compounds.

[13a] Matoush and Basolo, *J. Am. Chem. Soc.* **78**, 3972 (1956).

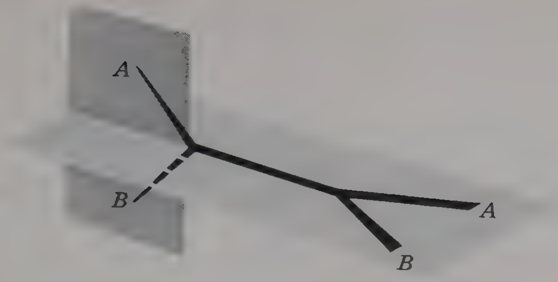
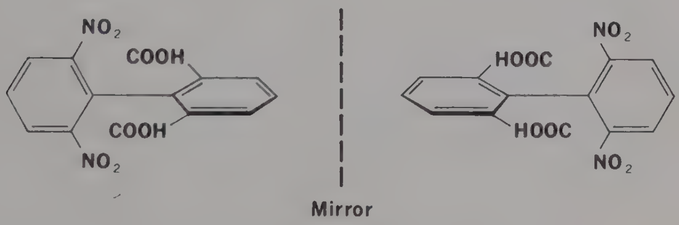


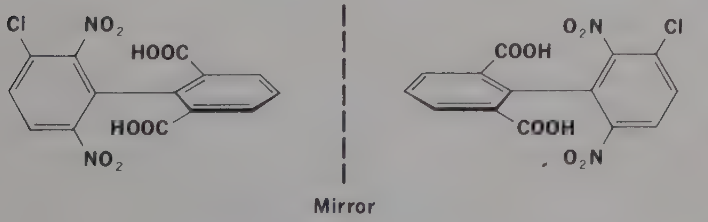
Figure 2. *Perpendicular disymmetric planes.*

pounds the two rings are in perpendicular planes. Three cases may be distinguished: both rings symmetric; one symmetric; neither symmetric. In the first case, e.g.,



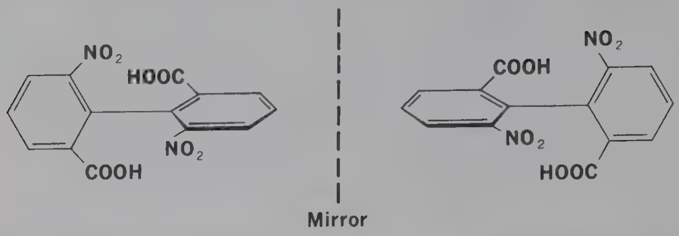
the molecule has two planes of symmetry. If a plane is drawn containing all atoms and groups in either ring, it is a *symmetrical* perpendicular bisector of the other ring. Such molecules are not optically active and, by the scheme in Figure 2, may be represented as *AA* · · · · · *BB*.

In the second case only one ring is symmetric:



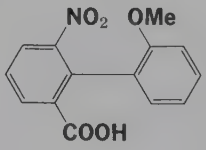
A plane drawn in the ring containing the nitro groups symmetrically bisects the other ring, but the plane of the ring containing the carboxyl groups is not a plane of symmetry. Nevertheless, one plane of symmetry is sufficient to make the compound optically inactive, and it is. The case may be symbolized as *AB* · · · · · *CC*.

In the third case neither ring is symmetric:



There is no plane of symmetry, and many such compounds have been resolved. This corresponds to $AB\cdots\cdots AB$. Of course $AB\cdots\cdots CD$ cases are also resolvable. It is important to note that, if *either* ring is symmetrical, the molecule has a plane of symmetry and is inactive and that groups in the para positions cannot cause dissymmetry.

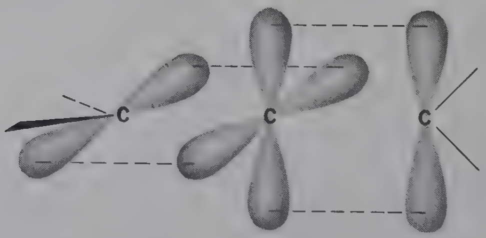
It is not always necessary for four large ortho groups to be present in order for rotation to be prevented. Compounds with three and even two groups, if large enough, can have hindered rotation and, if suitably substituted, can be resolved. An example is biphenyl-2,2′-bissulfonic acid.[14] In some cases, the groups may be large enough to slow rotation greatly, but not prevent it completely. In such cases, optically active compounds may be prepared which slowly racemize on standing. Thus, **7** loses its optical activity with a half-life of 9.4 min in ethanol at 25°.[15] Compounds with greater rotational stability can often be racemized if higher temperatures are used to supply the energy necessary to force the groups past each other.



7

Many analogous cases are known, where optical activity arises from hindered rotation of other types of aromatic ring: e.g., binaphthyls, bipyrryls, etc.

In allenes the central carbon is *sp* bonded. The remaining two *p* orbitals are perpendicular to each other, and each overlaps with the *p* orbital of one

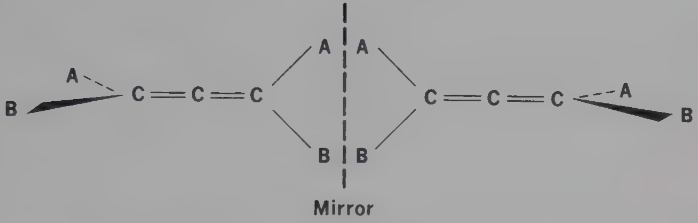


---

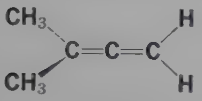
[14] Patterson and Adams, *J. Am. Chem. Soc.* **57**, 762 (1935).

[15] Stoughton and Adams, *J. Am. Chem. Soc.* **54**, 4426 (1952).

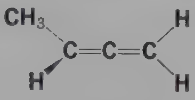
adjacent carbon atom, forcing the two remaining bonds of each carbon into perpendicular planes. Thus allenes fall into the category represented by Figure 2:



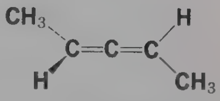
Like biphenyls, allenes are resolvable only if both sides are dissymmetric. Compounds corresponding to the three biphenyl cases are


Inactive

AA..........BB


Inactive

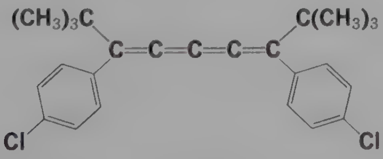
AB..........CC


Active

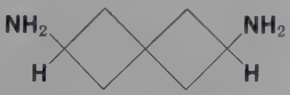
AB..........AB

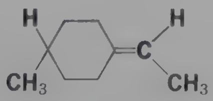
These cases are completely different from the cis-trans isomerism of compounds with one double bond (p. 94). In the latter cases the four groups are all in one plane, the isomers are not enantiomers, and neither is optically active, while in allenes the groups are in two perpendicular planes, and the isomers are a pair of optically active enantiomers.

When three, five, or any *odd* number of cumulative double bonds exist, orbital overlap causes the four groups to occupy one plane, and cis-trans isomerism is observed. When four, six, or any *even* number of cumulative double bonds exist, the situation is analogous to that in the allenes, and optical activity is possible. **8** has been resolved.[16]


8

Among other types of compounds which contain the system illustrated in Figure 2 and which similarly exhibit optical activity if they are *AB*·····*AB*-substituted are spiranes (for example, **9**) and compounds with exocyclic double bonds (for example, **10**).

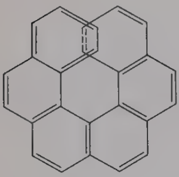

9


10

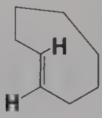
---

[16] Nakagawa, Shingū, and Naemura, *Tetrahedron Letters* **1961**, 802.

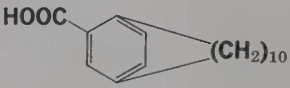
5. *Dissymmetry due to a helical shape.* Several compounds have been prepared which are optically active because they have a shape which is actually helical and can therefore be left- or right-handed in orientation. The entire molecule is usually less than one full turn of the helix, but this does not alter the possibility of left- and right-handedness. An example is hexihelicene[17] (**11**), in which one side of the molecule must lie above the other because of crowding. Another is *trans*-cyclooctene (**12**) (see p. 96), in which the carbon chain must lie above the plane of the double bond on one side and below it on the other.[18]



11

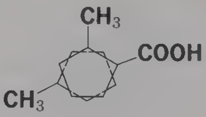


12

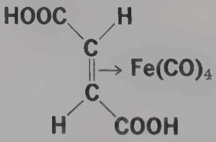


13

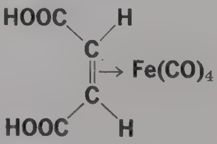
6. *Dissymmetry caused by restricted rotation of other types.* Substituted paracyclophanes may be optically active, and **13**, for example, has been resolved.[19] In this case dissymmetry results because the benzene ring cannot rotate so that the carboxyl group goes through the alicyclic ring. Ferrocenes which are substituted with at least two different groups on one ring display optical isomerism. For example, **14** has been resolved.[20] Other metallic complexes of suitable geometry are also nonsuperimposable on their mirror images and hence resolvable. For example, fumaric acid–iron–tetracarbonyl (**15**) has been resolved.[21] The corresponding maleic acid compound (**16**) has a plane of symmetry and is not resolvable.



14



15



16

---

[17] Newman and Lednicer, *J. Am. Chem. Soc.* **78,** 4765 (1956).

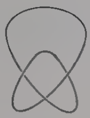
[18] Cope, Ganellin, Johnson, Van Auken, and Winkler, *J. Am. Chem. Soc.* **85,** 3276 (1963). Also see Cope, Banholzer, Keller, Pawson, Whang, and Winkler, *J. Am. Chem. Soc.* **87,** 3644 (1965).

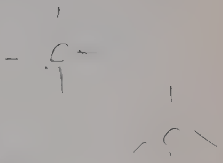
[19] Blomquist, Stahl, Meinwald, and Smith, *J. Org. Chem.* **26,** 1687 (1961).

[20] Westman and Rinehart, *Acta Chem. Scand.* **16,** 1199 (1962).

[21] Paiaro, Palumbo, Musco, and Panunzi, *Tetrahedron Letters* **1965,** 1067; also see Paiaro and Panunzi, *J. Am. Chem. Soc.* **86,** 5148 (1964).

An interesting type of optical isomerism has been proposed, though no example is yet known.[22] Rings containing 50 or more members should be able to exist as knots:





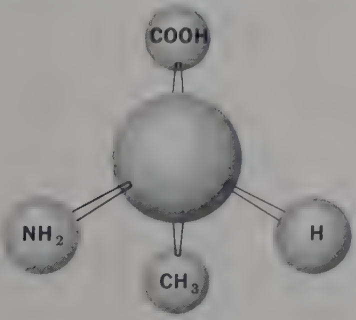
Such a knot would be nonsuperimposable on its mirror image.

Creation of an Asymmetric Center. Any structural feature of a molecule which gives rise to optical activity may be called an asymmetric center. In many reactions a new asymmetric center is created, for example,

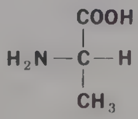
$$CH_3CH_2COOH + Br_2 \xrightarrow{P} CH_3CHBrCOOH$$

If the reagents and reaction conditions are all symmetric, then the product must be a racemic mixture. No optically active material can be created if all starting materials and conditions are optically inactive.[23] This statement also holds when one begins with a racemic mixture. Thus racemic 2-butanol, treated with HBr, must give racemic 2-bromobutane.

The Fischer Projection. For a thorough understanding of stereochemistry it is useful to examine molecular models (like those depicted in Figure 1). However, when writing on paper or on the blackboard this is not feasible, and Emil Fischer greatly served the interests of chemistry by inventing, in 1891, the Fischer projection method of representing tetrahedral carbons on paper. By this convention, the model is held so that the two bonds in front of the paper are horizontal, and those behind the paper are vertical:



≡



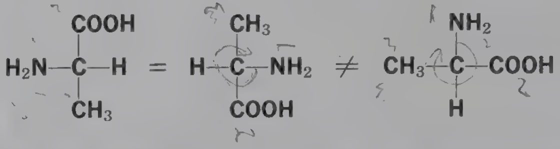
$$\begin{array}{c} COOH \\ | \\ H_2N-C-H \\ | \\ CH_3 \end{array}$$

---

[22] Frisch and Wasserman, *J. Am. Chem. Soc.* **83**, 3789 (1961).

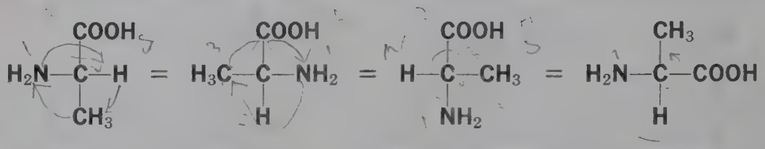
[23] There is one exception to this statement. In a very few cases racemic mixtures may crystallize from solution in such a way that all of the (+) molecules go into one crystal and the (−) molecules into another. If one of the crystals crystallizes before the other, then a rapid filtration results in optically active material.

In order to obtain proper results from these formulas, it should be remembered that they are projections and must be treated differently from the models in testing for superimposability. Every plane is superimposable on its mirror image; hence with these formulas there must be added the restriction that they may not be taken out of the plane of the blackboard or paper. Also they may not be rotated 90°, though 180° rotation is permissible.



$$\begin{array}{c}\text{COOH}\\ |\\ \text{H}_2\text{N}-\text{C}-\text{H}\\ |\\ \text{CH}_3\end{array} = \begin{array}{c}\text{CH}_3\\ |\\ \text{H}-\text{C}-\text{NH}_2\\ |\\ \text{COOH}\end{array} \neq \begin{array}{c}\text{NH}_2\\ |\\ \text{CH}_3-\text{C}-\text{COOH}\\ |\\ \text{H}\end{array}$$

It is also permissible to keep any one group fixed and to rotate the other three clockwise or counterclockwise (because this can be done with models):



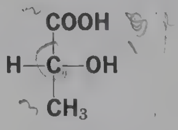
$$\begin{array}{c}\text{COOH}\\ |\\ \text{H}_2\text{N}-\text{C}-\text{H}\\ |\\ \text{CH}_3\end{array} = \begin{array}{c}\text{COOH}\\ |\\ \text{H}_3\text{C}-\text{C}-\text{NH}_2\\ |\\ \text{H}\end{array} = \begin{array}{c}\text{COOH}\\ |\\ \text{H}-\text{C}-\text{CH}_3\\ |\\ \text{NH}_2\end{array} = \begin{array}{c}\text{CH}_3\\ |\\ \text{H}_2\text{N}-\text{C}-\text{COOH}\\ |\\ \text{H}\end{array}$$

However, the *interchange* of any two groups results in the conversion of an enantiomer into its mirror image (this applies to models as well as to the Fischer projections).

With these restrictions Fischer projections may be used instead of models to test whether a molecule containing asymmetric carbons is superimposable on its mirror image. However, there are no such conventions for molecules whose dissymmetry arises from anything other than asymmetric atoms, and when such molecules are examined on paper, three-dimensional pictures must be used, and there are no restrictions about the plane of the paper.

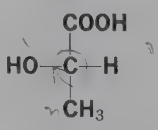
atoms

Absolute Configuration. Suppose we have two test tubes, one containing (−)-lactic acid, and the other the (+) enantiomer. One test tube contains **17** and the other **18**. How do we know which is which? Chemists in the early part of this century pondered this problem and decided that they could not know, not for lactic acid nor for any other compound. Therefore Rosanoff proposed that one compound be chosen as a standard, and a configuration be



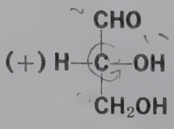
$$\begin{array}{c}\text{COOH}\\ |\\ \text{H}-\text{C}-\text{OH}\\ |\\ \text{CH}_3\end{array}$$

17



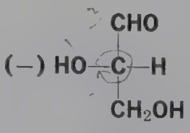
$$\begin{array}{c}\text{COOH}\\ |\\ \text{HO}-\text{C}-\text{H}\\ |\\ \text{CH}_3\end{array}$$

18



$$(+)\,\begin{array}{c}\text{CHO}\\ |\\ \text{H}-\text{C}-\text{OH}\\ |\\ \text{CH}_2\text{OH}\end{array}$$

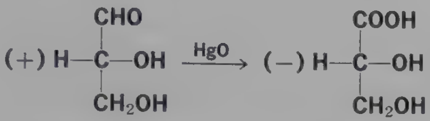
19



$$(-)\,\begin{array}{c}\text{CHO}\\ |\\ \text{HO}-\text{C}-\text{H}\\ |\\ \text{CH}_2\text{OH}\end{array}$$

20

arbitrarily assigned to it. The compound chosen was glyceraldehyde because of its relationship to the sugars. The (+) isomer was assigned the configuration shown in **19**, and it was given the label D. The (−) isomer, designated to be **20**, was given the label L. Once a standard was chosen, other compounds could then be related to it. For example, (+)-glyceraldehyde, oxidized with mercuric oxide, gives (−)-glyceric acid:



$$(+)\ \mathrm{H{-}\overset{\displaystyle CHO}{\underset{\displaystyle CH_2OH}{C}}{-}OH} \xrightarrow{\mathrm{HgO}} (-)\ \mathrm{H{-}\overset{\displaystyle COOH}{\underset{\displaystyle CH_2OH}{C}}{-}OH}$$

Since it is highly improbable that the configuration at the central carbon changed, it may be concluded that (−)-glyceric acid has the same configuration as (+)-glyceraldehyde, and therefore (−)-glyceric acid is also called D. This example emphasizes that molecules with the same configuration need not rotate the plane of polarized light in the same direction. This fact should not surprise us when we remember that the same compound can rotate the plane in opposite directions under different conditions.

Once the configuration of the glyceric acids was known (in relation to the glyceraldehydes), it was then possible to relate other compounds to either of these, and each time a new compound was related, others could be related to *it*. In this way many thousands of compounds have now been related, indirectly, to D- or L-glyceraldehyde, and it has been determined that **17**, which has the D configuration, is the isomer which rotates the plane of polarized light to the left. Even compounds without asymmetric atoms, such as biphenyls[24] and allenes[25] have been placed in the D or L series.[26] When a compound has been placed in the D or L series, its *absolute configuration* is said to be known.

In 1951 it became possible to determine whether Rosanoff's guess had been right. Ordinary x-ray crystallography is powerless to distinguish between a D and an L isomer, but by use of a special technique, Bijvoet was able to examine sodium rubidium tartrate and found that Rosanoff had made the correct choice.[27] By this time the fact was interesting to know, but it would have made no difference to organic chemists if he had made the wrong choice, since this would not have affected the important thing, which is the relationship of one compound to another. It was perhaps historically fitting that the first true absolute configuration should have been determined on a salt of tartaric acid, since Pasteur made his great discoveries on another salt of this acid.

In spite of the widespread use of D and L to denote absolute configuration, the method is not without faults. The designation of a particular enantiomer as D or L often depends on which compounds it is related to. Examples are known where an enantiomer can, by five or six steps, be related to a known D compound, and by five or six other steps, be related to the L enantiomer of the same compound. In a case of this sort, an arbitrary choice of D or L must be used.

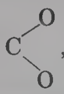
---

[24] Newman, Rutkin, and Mislow, *J. Am. Chem. Soc.* **80**, 465 (1958).

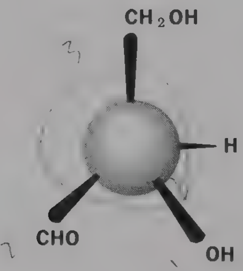
[25] Eliel, *Tetrahedron Letters* **1960**, No. 8, 16; Jones, Loder, and Whiting, *Proc. Chem. Soc.* **1960**, 180.

[26] The use of small *d* and *l* is now discouraged, since some authors used it for rotation, and some for configuration. However, a racemic mixture is still a *dl* mixture, since there is no ambiguity here.

[27] Bijvoet, Peerdeman, and van Bommel, *Nature* **168**, 271 (1951).

Because of this and other flaws, another system, the *Cahn-Ingold-Prelog* system, has been devised. In this system, the four groups on the asymmetric carbon are ranked according to a set of sequence rules.[28] For our purposes we may confine ourselves to the first three of these rules: (1) substituents are listed in order of decreasing atomic number of the atom directly joined to the carbon; (2) where two or more of the atoms connected to the asymmetric carbon are the same, then the atomic number of the second atom determines the order, or if two of these atoms are the same, then the one which has more substituents of higher atomic number takes precedence; and (3) C=O is counted as if it were , and similarly for other double bonds.

Thus the four groups of glyceraldehyde are to be arranged in the sequence: OH, CHO, CH_2OH, H. Once the order is determined, the molecule is held so that the lowest group in the sequence is pointed away from the viewer. Then, if the other groups, in the order listed, are oriented clockwise, the molecule is designated R, and if counterclockwise, S. For glyceraldehyde, the (+) enantiomer is R:



The Cahn-Ingold-Prelog system is unambiguous and easily applicable in most cases. Whether to call an enantiomer R or S does not depend on correlations, but of course the configuration must be known before the system can be applied, and this does depend on correlations.

Methods of Determining Configuration[29]

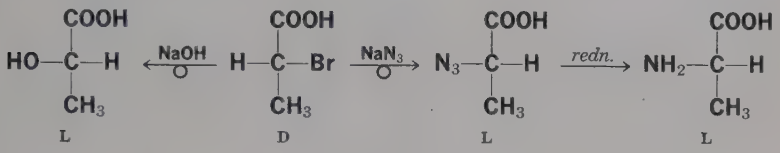
1. Conversion of the unknown to, or formation of the unknown from, a compound of known configuration without disturbing the asymmetric center. See the glyceraldehyde–glyceric acid example above (p. 83).

---

[28] For a description of the system, and sets of sequence rules, see Cahn, Ingold, and Prelog, *Angew. Chem. Intern. Ed. Engl.* **5**, 385–415 (1966), *Experientia* **12**, 81 (1956); and Cahn, *J. Chem. Educ.* **41**, 116 (1964). See also Hanson, *J. Am. Chem. Soc.* **88**, 2731 (1966).

[29] For reviews, see Schlenk, *Angew. Chem. Intern. Ed. Engl.* **4**, 139–145 (1965); and Mills and Klyne, *Progr. Stereochem.* **1**, 177–222 (1954).

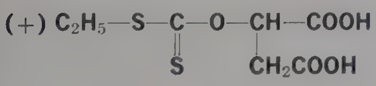
2. Conversion at the asymmetric center, if the mechanism is known. Thus, the S_N2 mechanism proceeds with inversion of configuration at an asymmetric carbon (see p. 252). It was by a series of such transformations that lactic acid was related to alanine (the symbol $\xrightarrow[\circ]{}$ is used to signify inversion of configuration):



$$\underset{\text{L}}{\text{HO}-\overset{\text{COOH}}{\underset{\text{CH}_3}{\text{C}}}-\text{H}} \xleftarrow[\circ]{\text{NaOH}} \underset{\text{D}}{\text{H}-\overset{\text{COOH}}{\underset{\text{CH}_3}{\text{C}}}-\text{Br}} \xrightarrow[\circ]{\text{NaN}_3} \underset{\text{L}}{\text{N}_3-\overset{\text{COOH}}{\underset{\text{CH}_3}{\text{C}}}-\text{H}} \xrightarrow{\textit{redn.}} \underset{\text{L}}{\text{NH}_2-\overset{\text{COOH}}{\underset{\text{CH}_3}{\text{C}}}-\text{H}}$$

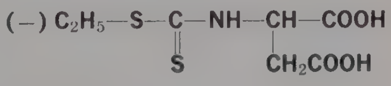
See also the discussion on pp. 252–254.

3. The method of quasi racemates.[30] It was mentioned (p. 72) that a solid racemic mixture often has a melting point which differs from that of the two enantiomers. In many such cases the molecules of the D isomer fit better into the lattice when they are next to molecules of L isomer, and there are fairly strong van der Waals forces between the D and L molecules. Such mixtures are known as *racemic compounds* and are recognizable by characteristic melting-point curves. In some cases it has been found that "racemic compounds" are formed between the D isomer of one compound and the L isomer of another compound which is similar to but not identical with the first. These *quasi racemates* are recognizable because their melting-point curves look like the curves of true racemic compounds. Mixtures are prepared of the unknown compound with known D and L forms of a similar compound. If the unknown is D, then the mixture with the known L may be a quasi racemate, but the mixture with the known D will not be. For example, two compounds which form a quasi racemate and hence have opposite configurations, are



$$(+)\ \text{C}_2\text{H}_5-\text{S}-\underset{\text{S}}{\underset{\|}{\text{C}}}-\text{O}-\underset{\text{CH}_2\text{COOH}}{\underset{|}{\text{CH}}}-\text{COOH}$$

and



$$(-)\ \text{C}_2\text{H}_5-\text{S}-\underset{\text{S}}{\underset{\|}{\text{C}}}-\text{NH}-\underset{\text{CH}_2\text{COOH}}{\underset{|}{\text{CH}}}-\text{COOH}$$

4. Biochemical methods. In a series of similar compounds, such as amino acids or certain types of steroids, a given enzyme will usually attack only those molecules with one kind of configuration. If the enzyme attacks only the L form of eight amino acids, say, then attack on the unknown ninth amino acid will also be on the L form.

5. Optical comparison. It is sometimes possible to use the sign and extent of rotation to determine which isomer has which configuration. In a homologous series, the rotation usually changes gradually and in one direction. If the configurations of enough members of the series are known, the configurations of the missing ones may be determined by extrapolation. Also certain groups contribute more or less fixed amounts to the rotation of the parent molecule, especially when the parent is a rigid system such as a steroid.

---

[30] For a review, see Fredga, *Tetrahedron* **8**, 126–144 (1960).

Other methods have also been used, including optical rotatory dispersion (see p. 110) and asymmetric synthesis (see p. 91). It must be remembered that no method is completely foolproof, and false assignments are sometimes made.

The Cause of Optical Activity. The question may be asked: just why does a dissymmetric molecule rotate the plane of polarized light? Theoretically, the answer to this question is known and in a greatly simplified form may be explained as follows:

Whenever any light hits any molecule in a transparent material, the light is slowed because of interaction with the molecule. This phenomenon on a gross scale is responsible for the refraction of light, and the decrease in velocity is proportional to the refractive index of the material. The extent of interaction is dependent on the polarizability of the molecule. Plane-polarized light may be regarded as being made up of two kinds of circularly polarized light. Circularly polarized light has the appearance (or would have, if one could see the wave) of a helix propagating around the axis of light motion, and one kind is a left-handed and the other a right-handed helix. As long as the plane-polarized light is passing through a symmetrical region, the two circularly polarized components travel at the same speed. However, a dissymmetric molecule has polarizability which is different depending on whether it is approached from the left or the right. One circularly polarized component approaches the molecule, so to speak, from the left and sees a different polarizability (hence on a gross scale, a different refractive index) than the other, and is slowed to a different extent. This would seem to mean that the left-handed and right-handed circularly polarized components travel at different velocities, since each has been slowed to a different extent. However, it is not possible for two components of the same light to be traveling at different velocities. What actually takes place, therefore, is that the faster component "pulls" the other toward it, resulting in rotation of the plane.[31] These ideas may be expressed mathematically, and in principle it is possible to calculate the sign and amount of rotation for any molecule (this represents an additional way of determining absolute configuration). However, it is necessary to use wave equations, and the limitations of these were discussed in Chapter 1. Hence, in practice, the sign and amount of rotation have been calculated for very few molecules, and the results have been wrong about as often as they have been right. Brewster[32] has devised a method of making such predictions based on the polarizabilities of the groups in the molecule, and this method has given fairly good results in many cases, though it falls down for certain classes of compounds.

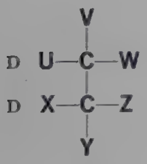
In liquids and gases the molecules are randomly oriented. A molecule which is optically inactive because it has a plane of symmetry will very seldom be oriented so that the plane of the polarized light coincides with the plane of symmetry. When it is so oriented, that particular molecule does not rotate the plane, but all others not oriented in that manner do rotate the plane, even though the molecules are symmetric. There is no net rotation because, the molecules being present in large number and randomly oriented, there will always be another molecule later on in the path of the light which is oriented exactly opposite, and so will rotate the plane back again. Even though nearly all molecules are rotating the plane individually, the total rotation is zero. For dissymmetric molecules, however (if there is no racemic mixture), there is no opposite orientation present, and there is a net rotation.

---

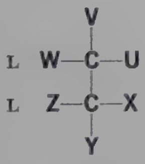
[31] For longer, nontheoretical discussions, see Eliel, Ref. 1, pp. 398–412, and Wheland, Ref. 1, pp. 204–211. For theoretical discussions, see Kauzmann, "Quantum Chemistry," pp. 616–635, Academic Press Inc., New York, 1957; Mason, *Quart. Rev. (London)* **17,** 20–66 (1963); and Liehr, *J. Phys. Chem.* **68,** 665, 3629 (1964).

[32] Brewster, *J. Am. Chem. Soc.* **81,** 5475, 5483, 5493 (1959).

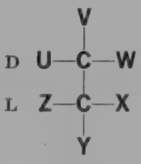
Molecules with More than One Asymmetric Center. When a molecule has two asymmetric centers, then each center has its own configuration. Each center may be classified R or S by the Cahn-Ingold-Prelog method, or each may be separately related to a known compound, or one of the centers may be related to the known and the second center related to the first, and the two centers in this manner may be classified D or L. In any event there is a total of four isomers, since the first center may be D or L, and so may the second.



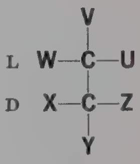
21



22



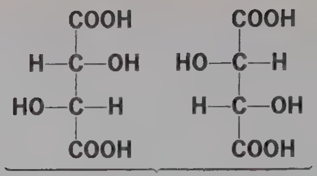
23

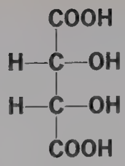


24

Since a molecule can have only one mirror image, only one of the other three can be the enantiomer of **21**. This is **22**. **23** and **24** are a second pair of enantiomers, and the relationship of these to **21** and **22** is designated by the term *diastereomer*. Diastereomers are classically defined as *nonenantiomeric pairs in a set which also contains optically active compounds.* (See also the definition given on p. 98.) **23** and **24**, being enantiomers, must have identical properties, except as noted on p. 71 and the same is true for **21** and **22**. However, the properties of **21** and **22** are not identical with those of **23** and **24**. They have different melting points, boiling points, solubilities, reactivity, and all other properties. The properties are usually *similar,* but not *identical.*

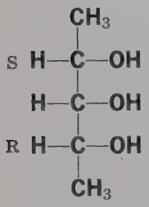
Although four is the usual (and the maximum possible) number of isomers when the compound has two asymmetric centers (dissymmetric compounds without an asymmetric carbon, or with one asymmetric carbon and another type of asymmetric center also follow the rules described here), some compounds have fewer. When the three groups on one asymmetric atom are the same as those on the other, then one of the isomers (called a *meso* form) has a plane of symmetry and hence is optically inactive, even though it has two asymmetric carbons. Tartaric acid is a typical case:


dl pair

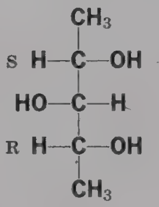

meso

There are only three isomers of tartaric acid: a pair of enantiomers and an inactive meso form.

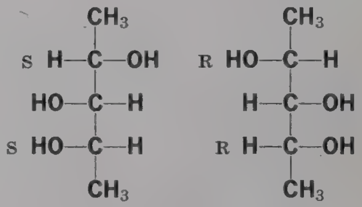
In most cases with more than two asymmetric centers, the number of isomers can be calculated from the formula 2^n, where n is the number of asymmetric centers, although in some cases the actual number is less than this, owing to meso forms. An interesting case is that of 2,3,4-pentanetriol (or any similar molecule). The middle carbon is not asymmetric when the 2- and 4-carbons are both R (or both S) but is asymmetric when one of them is R and the other S. Such a carbon is called a *pseudoasymmetric* carbon. In these cases there are four isomers: two meso forms and one *dl* pair:



meso



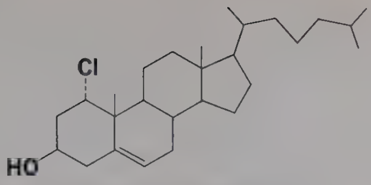
meso



dl pair

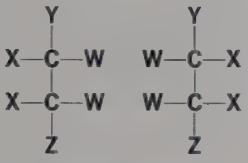
The student should satisfy himself, remembering the rules governing use of the Fischer projections, that these isomers are different, that the meso forms are superimposable on their mirror images, and that there are no other stereoisomers.

The problem arises how to name the different stereoisomers of a compound when there are more than two. Enantiomers are virtually always called by the same name, being distinguished by R and S, or D and L, or (+) and (−). In the early days of organic chemistry, it was customary to give each pair of enantiomers a different name, or at least a different prefix (such as *epi*, *peri*, etc.). Thus the aldohexoses are called glucose, mannose, idose, etc., though they are all 2,3,4,5,6-pentahydroxyhexanal. This practice was partially due to lack of knowledge of which isomers had which configurations. In recent years it has been customary to describe *each asymmetric position* separately, as either R or S, or D or L, or, in special fields, using other symbols. Thus, in the case of steroids, groups above the "plane" of the ring system are designated β, and those below it α. Solid lines are used to depict β groups, and dotted lines for α groups. An example is



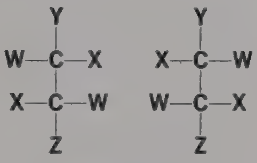
1α-Chloro-5-cholesten-3β-ol

For many open-chain compounds prefixes are used which are derived from the names of the corresponding sugars and which describe the whole system rather than each asymmetric center separately. Two such prefixes in common use are *erythro* and *threo*, which are applied to systems containing two asymmetric carbons when two of the groups are the same and the third is different.



$$\begin{array}{ccc} & \text{Y} & \\ & | & \\ \text{X}- & \text{C} & -\text{W} \\ & | & \\ \text{X}- & \text{C} & -\text{W} \\ & | & \\ & \text{Z} & \end{array} \qquad \begin{array}{ccc} & \text{Y} & \\ & | & \\ \text{W}- & \text{C} & -\text{X} \\ & | & \\ \text{W}- & \text{C} & -\text{X} \\ & | & \\ & \text{Z} & \end{array}$$

erythro *dl* pair

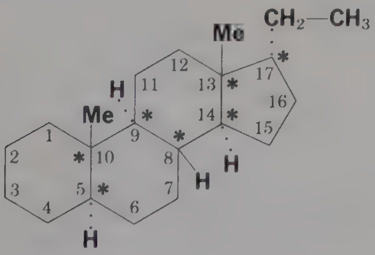


$$\begin{array}{ccc} & \text{Y} & \\ & | & \\ \text{W}- & \text{C} & -\text{X} \\ & | & \\ \text{X}- & \text{C} & -\text{W} \\ & | & \\ & \text{Z} & \end{array} \qquad \begin{array}{ccc} & \text{Y} & \\ & | & \\ \text{X}- & \text{C} & -\text{W} \\ & | & \\ \text{W}- & \text{C} & -\text{X} \\ & | & \\ & \text{Z} & \end{array}$$

threo *dl* pair

The erythro pair has the identical groups on the same side when drawn in the Fischer convention, and if Y were changed to Z, it would be meso. The threo pair has them on opposite sides and, if Y were changed to Z, would still be a *dl* pair.

An interesting naming system has been proposed based on the binary number concept.[33] This would assign the value 1 or 0 to each asymmetric center (corresponding to D or L, R or S, α or β, etc.) and then convert the binary number so formed to an ordinary number which would be the prefix. Thus the compound 5α,17α-pregnane



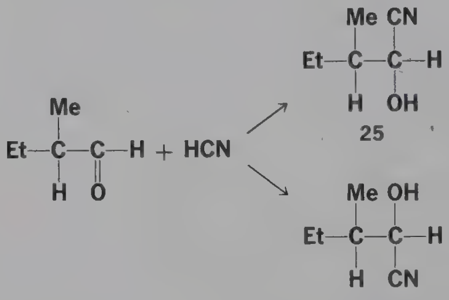
has seven asymmetric carbons (starred) which in order of the usual steroid numbering, would be 0101100, if an α and a β group are assigned the values 0 and 1, respectively. This binary number is equal to 44, and the compound would be called /44/-pregnane. The system is unambiguous, since each binary number corresponds to one and only one ordinary number.

---

[33] Feldman, *J. Org. Chem.* **24**, 1556 (1959).

Asymmetric Synthesis. As mentioned before, optically active materials cannot be created from inactive starting materials and conditions; hence true asymmetric synthesis is impossible, except in the manner previously noted.[23] However, when a new asymmetric center is created, the two possible configurations need not be formed in equal amounts if anything is present which is dissymmetric. Such syntheses are usually called *asymmetric syntheses* and may be discussed under four headings.

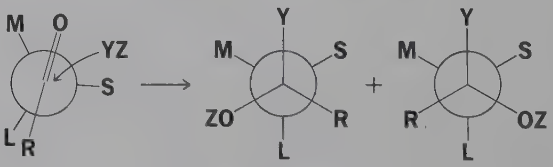
1. *Active substrate.* If a new asymmetric center is created in a molecule which is already optically active, then the two diastereomers are not (except fortuitously) formed in equal amounts.



25

26

The reason is that the direction of attack by the reagent is determined by the groups already there. For certain additions to the carbon-oxygen double bond of ketones containing an asymmetric α-carbon, *Cram's rule* predicts which diastereomer will predominate.[34] If the molecule is observed along its axis, it may be represented as in **27** (see p. 102), where S, M, and L stand



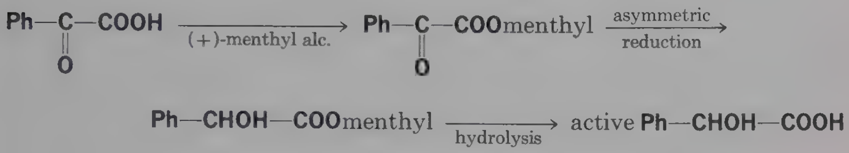
27 Major product Minor product

for small, medium, and large, respectively. The oxygen of the carbonyl orients itself so as to be between the small- and the medium-sized groups. The rule is that the incoming group preferentially attacks on the side of the plane containing the small group. By this rule, it may be predicted that **26** will be formed in larger amount than **25**.

---

[34] Cram and Elhafez, *J. Am. Chem. Soc.* **74,** 5828 (1952); Cram and Kopecky, *J. Am. Chem. Soc.* **81,** 2748 (1959).

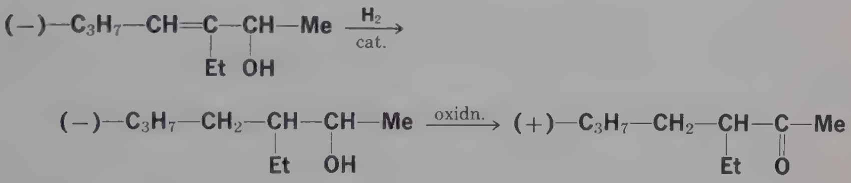
Many reactions of this type are known, in some of which the extent of favoritism approaches 100%. The farther away the reaction site is from the asymmetric center, the less influence the latter has, and the more equal are the amounts of diastereomers formed. In some cases the product may be easily cleaved at a point between the old asymmetric center and the new one. It is not surprising that in a case such as



$$\mathrm{Ph{-}\underset{\underset{O}{\|}}{C}{-}COOH} \xrightarrow[\text{(+)-menthyl alc.}]{} \mathrm{Ph{-}\underset{\underset{O}{\|}}{C}{-}COO}\text{menthyl} \xrightarrow[\text{reduction}]{\text{asymmetric}}$$

$$\mathrm{Ph{-}CHOH{-}COO}\text{menthyl} \xrightarrow[\text{hydrolysis}]{} \text{active } \mathrm{Ph{-}CHOH{-}COOH}$$

an investigator may feel that he has actually carried out an asymmetric synthesis. Another set of reactions which seems at first glance uncanny also involves the use of one asymmetric center to create another with subsequent destruction of the first, though in this case without cleavage.[35]



$$(-){-}\mathrm{C_3H_7{-}CH{=}\underset{\underset{Et}{|}}{C}{-}\underset{\underset{OH}{|}}{CH}{-}Me} \xrightarrow[\text{cat.}]{\mathrm{H_2}}$$

$$(-){-}\mathrm{C_3H_7{-}CH_2{-}\underset{\underset{Et}{|}}{CH}{-}\underset{\underset{OH}{|}}{CH}{-}Me} \xrightarrow{\text{oxidn.}} (+){-}\mathrm{C_3H_7{-}CH_2{-}\underset{\underset{Et}{|}}{CH}{-}\underset{\underset{O}{\|}}{C}{-}Me}$$

2. *Active reagent.* A pair of enantiomers may be separated by an active reagent which reacts with one of them faster than it does with the other (this is also a method of resolution). If the absolute configuration of the reagent is known, then the configuration of the enantiomers may often be determined by a knowledge of the mechanism, and by an examination of which diastereomer is preferentially formed.[36] Creation of a new asymmetric center in an inactive molecule may also be accomplished with an active reagent, though it is rare for 100% selectivity to be observed. An example[37] is reduction of butanone with a complex of $\mathrm{LiAlH_4}$ and certain glucose derivatives, to give 2-butanol with up to 15% optical activity.

3. *Active catalyst or solvent.* A few such examples are present in the literature, for instance, the preparation of optically active (though not optically pure) secondary alcohols by the reduction of unsymmetrical ketones with hydrogen over a nickel catalyst treated with optically active amino acids;[38] the conversion of benzaldehyde to optically active mandelonitrile by treatment with HCN in the presence of an enzyme;[39] and the preparation of

[35] Arcus and Smyth, *J. Chem. Soc.* **1955**, 34.

[36] Horeau, *Tetrahedron Letters* **1961**, 506.

[37] Landor, Miller, and Tatchell, *Proc. Chem. Soc.* **1964**, 227. For a review of asymmetric reductions, see Morrison, *Surv. Progr. Chem.* **3**, 147–182 (1966).

[38] Izumi, Imaida, Fukawa, and Akabori, *Bull. Chem. Soc. Japan* **36**, 21, 155 (1963); Tatsumi, Imaida, Fukuda, Izumi, and Akabori, *Bull. Chem. Soc. Japan* **37**, 846 (1964).

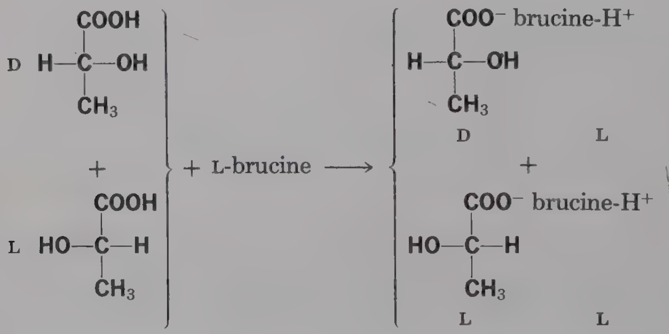
[39] Wheland, Ref. 1, p. 323.

optically active alcohols by the treatment of Grignard reagents with aldehydes in optically active ether solvents.[40]

4. *Reactions in the presence of circularly polarized light.*[41] This is an interesting idea, but the results have been meager. In a few cases mixtures with slight rotations (less than 1°) have been obtained.

Methods of Resolution. A pair of enantiomers may be separated in several ways, of which conversion to diastereomers and separation of these by fractional crystallization is by far the most often used. In this method, and in some of the others, both isomers may be recovered, but in some methods it is necessary to destroy one.

1. *Conversion to diastereomers.* If the racemic mixture to be resolved contains a carboxyl group (and no strongly basic group), then it is possible to form a salt with an optically active base. Since the base used is, say, the L form, there will be a mixture of two salts produced having the configurations LL and DL:



Although the acids are enantiomers, the salts are diastereomers and have different properties. The property which is most often utilized is differential solubility. The mixture of diastereomeric salts is allowed to crystallize from a suitable solvent. Since the solubilities are different, the initial crystals formed will be richer in one diastereomer. Filtration at this point will already have achieved a partial resolution. Unfortunately, the difference in solubilities is rarely if ever great enough to effect total separation with one crystallization. Usually fractional crystallizations must be used, and the process is long and tedious. Nevertheless, it is the best general method known. Fortunately, naturally occurring optically active bases (mostly alkaloids) are readily available. Among the most commonly used are brucine, ephedrine, strychnine, and morphine. Once the two diastereomers have been separated, it is easy to convert the salts back to the free acids, and the recovered base can be used again.

Most resolution is done on carboxylic acids, and often, when a molecule does not contain a carboxyl group, it is converted to a carboxylic acid before resolution is attempted. However, the principle of conversion to diastereomers is not confined to carboxylic acids, and other groups may serve as handles to be coupled to an optically active reagent. Racemic bases may be converted to diastereomeric salts with active acids. Alcohols may be converted to diastereomeric esters, aldehydes to diastereomeric hydrazones, etc. Even hydrocarbons can be converted to diastereomeric inclusion compounds with optically active decxycholic acid (see p. 70), or even with urea.[42] Urea is not dissymmetric, but the cage structure is. *trans*-Cyclooctene (**12**) was resolved by conversion to a platinum complex containing an optically active amine.[18]

---

[40] See, for example, Blomberg and Coops, *Rec. trav. chim.* **83**, 1083 (1964).

[41] For a review, see Ulbricht, *Quart. Rev.* (*London*) **13**, 48–60 (1959).

Although fractional crystallization is by far the most common method for the separation of diastereomers, its tediousness, and the fact that it is limited to solids, have prompted a search for other methods. In the past these have not proved very useful. Fractional distillation has given only limited separation. Vapor-phase chromatography has been more successful,[43] and its use will undoubtedly increase.

2. *Differential absorption.* When a racemic mixture is placed on a chromatographic column, if the column consists of optically active substances, then in principle the enantiomers should move down the column at different rates and should be separable without the necessity of conversion to diastereomers. This has been successfully accomplished with paper and column chromatography. For example, DL-mandelic acid has been almost completely resolved by column chromatography on starch,[44] and DL-cysteine has been resolved by paper chromatography.[45] The cellulose in the paper is, of course, optically active. Separations involving gas chromatography with a column packed with an optically active absorbent have only recently been accomplished.[46]

3. *Biochemical processes.* The optically active compound which reacts at different rates with the two enantiomers may be present in a living organism. For instance, a certain bacterium may digest one enantiomer and not the other. This method is limited, since it is necessary to find the proper organism and since one of the enantiomers is destroyed in the process. However, when the proper organism is found, then the method leads to a high extent of resolution, since biological processes are usually very stereoselective.

4. *Mechanical separation.* This is the method by which Pasteur proved that racemic acid was actually a mixture of (+)- and (−)-tartaric acids.[47]

---

[42] For a summary of methods used to resolve particular types of compounds, see Eliel, Ref. 1, pp. 49–63.

[43] See, for example, Casanova and Corey, *Chem. Ind. (London)* **1961,** 1664; Gil-Av and Nurok, *Proc. Chem. Soc.* **1962,** 146; Gault and Felkin, *Bull. Soc. chim. France* **1965,** 742; Gil-Av, Charles, and Fischer, *J. Chromatog.* **17,** 408 (1965); Vitt, Saporovskaya, Gudkova, and Belikov, *Tetrahedron Letters* **1965,** 2575.

[44] Ohara, Fujita, and Kwan, *Bull. Chem. Soc. Japan* **35,** 2049 (1962); Ohara, Ohta, and Kwan, *Bull. Chem. Soc. Japan* **37,** 76 (1964).

[45] de Ligny, Nieboer, de Vijlder, and van Willigen, *Rec. trav. chim.* **82,** 213 (1963).

[46] Gil-Av, Feibush, and Charles-Sigler, *Tetrahedron Letters* **1966,** 1009.

[47] Besides discovering this method of resolution, Pasteur also discovered the method of conversion to diastereomers and separation by fractional crystallization and the method of biochemical separation.

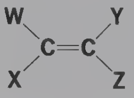
In the case of DL-sodium ammonium tartrate the enantiomers crystallize separately, all the (+) molecules going into one crystal and all the (−) into another. Since the crystals too are nonsuperimposable, their appearance is not identical, and a trained crystallographer can separate them with tweezers.[48] However, this is seldom a practical method, since few compounds are known which crystallize in this manner. Even sodium ammonium tartrate does so only when it is crystallized below 27°. A more useful variation of the method, though still not very common, is the seeding of a racemic solution with something which will cause only one enantiomer to crystallize.[49]

5. *Differential reactivity.* Since enantiomers react with optically active compounds at different rates, it is sometimes possible to effect a partial separation by stopping the reaction before completion. This method is very similar to the asymmetric syntheses discussed on p. 91.

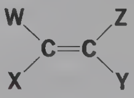
GEOMETRICAL ISOMERISM

Compounds in which rotation is restricted may exhibit geometrical isomerism.[50] These compounds do not rotate the plane of polarized light (unless they also happen to be dissymmetric), and the properties of the isomers are not identical. The two most important types are isomerism resulting from double bonds and that resulting from rings.

Geometrical Isomerism Resulting from Double Bonds. It has been mentioned (p. 14) that the two carbon atoms of a C=C double bond and the four atoms directly attached to them are all in the same plane and that rotation around the double bond is prevented. This means that in the case of a molecule WXC=CYZ, isomerism exists when W ≠ X and Y ≠ Z. There are two and only two isomers (**28** and **29**), each superimposable on its mirror image unless one of the groups happens to carry an asymmetric center. The two isomers are called cis and trans. When W = Y, then **28** is the cis and **29** the trans isomer, except as noted below. When all four groups are different, there is no rule about which is which, and a convention must be established in each case, except that in the case of double bonds in a carbon chain, the cis isomer is the one in which the groups containing the longest



28



29

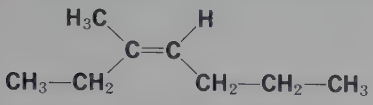
---

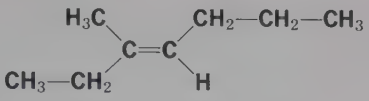
[48] This is a case of optically active materials arising from inactive materials. However, it may be argued that an optically active investigator is required to use the tweezers. Perhaps a hypothetical human being constructed entirely of inactive molecules would be unable to tell the difference between left- and right-handed crystals.

[49] For a review of the seeding method, see Secor, *Chem. Rev.* **63**, 297 (1963).

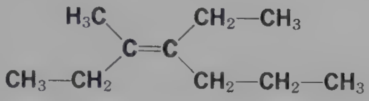
[50] For a review, see Crombie, *Quart. Rev.* (*London*) **6**, 101–140 (1952).

carbon chain are on the same side of the double bond, for example,

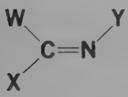

cis-3-Methyl-3-heptene

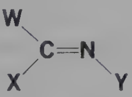

trans-3-Methyl-3-heptene

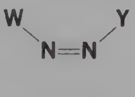
It may be seen that in some cases this rule conflicts with the rule given earlier. Thus, *cis*-3-methyl-4-ethyl-3-heptene has the two ethyl groups on opposite sides of the double bond:

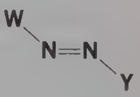


This type of isomerism is also possible with other double bonds, such as C=N, N=N, or even C=S,[51] although in these cases there are only two or three groups connected to the double-bond atoms. In the case of imines, oximes, and other C=N compounds, if W = Y, **30** is usually called syn and **31** anti, though the prefixes cis and trans are sometimes used here too. In azo compounds there is no ambiguity, and **32** is always cis or syn regardless of the nature of W and Y.

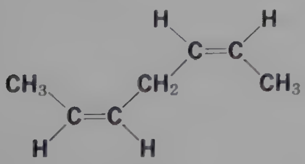

30

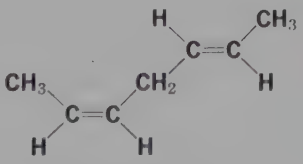

31

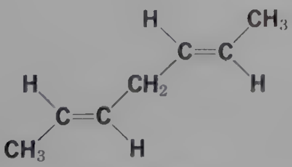

32



If there is more than one double bond in a molecule and if, for each, W ≠ Y and Y ≠ Z, then the number of isomers is, in the most general case, 2^n, although this number may be decreased if some of the substituents are the same, as in this example,


cis-cis

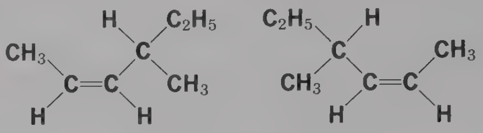

cis-trans


trans-trans

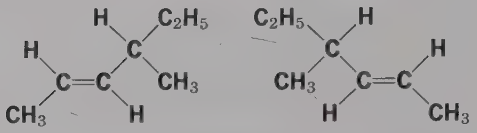
---

[51] King and Durst, *J. Am. Chem. Soc.* **85**, 2676 (1963).

Of course, allenes do not show cis-trans isomerism at all (see p. 78). When a molecule contains a double bond and an asymmetric carbon, there are four isomers, a cis pair of enantiomers and a trans pair:



cis *dl* pair



trans *dl* pair

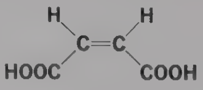
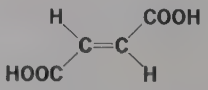
Double bonds in small rings are so constrained that they must be cis. From cyclopropene (a known system) to cycloheptene, double bonds in a ring cannot be trans. However, the cyclooctene ring is large enough to permit trans double bonds to exist (see **12**, p. 80), and for rings larger than 10- or 11-membered, trans isomers are more stable.[52]

Geometric isomers always differ in properties; the differences may range from very slight to considerable. The properties of maleic acid are so different from those of fumaric acid (Table 1) that it is not surprising that they have different names. Since they generally have more symmetry than cis isomers, trans isomers usually have higher melting points and lower solubilities in inert solvents. The cis isomer usually has a higher heat of combustion, which indicates a lower thermochemical stability. For this reason, cis compounds can often be transformed into the trans isomers by heating, which at a high enough temperature supplies enough energy to cause rotation about the double bond. Since this is a process leading to thermody-

---

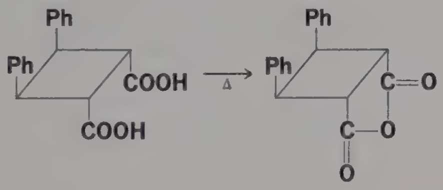
[52] Cope, Moore, and Moore, *J. Am. Chem. Soc.* **81**, 3153 (1959).

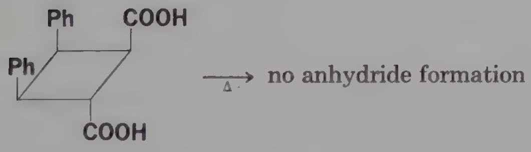
TABLE 1. Some properties of maleic and fumaric acids

Property	 *Maleic acid*	 *Fumaric acid*
Melting point	130°	286°
Solubility in water at 25°	788 g/liter	7 g/liter
$K_1(25°)$	1.5×10^{-2}	1×10^{-3}
$K_2(25°)$	2.6×10^{-7}	3×10^{-5}

namic equilibrium, trans compounds can seldom be converted to the cis isomers in this manner.[53] Other noticeably different properties are densities, acid strengths, boiling points, and various types of spectra, but the differences are too involved to be discussed here. It should be emphasized that the principles discussed in this paragraph are no more than general rules and that many exceptions are known.

There are many ways of telling which of a pair of isomers is cis and which is trans. The most dependable are x-ray and electron diffraction, though these methods have not often been used for this purpose. Other physical methods include infrared, ultraviolet, and nuclear-magnetic-resonance spectra (see Chapter 6), the measurement of dipole moments (a trans isomer of the type WYC=CWY has no dipole moment, while the cis isomer usually has one), and a comparison of melting points, solubilities, etc., according to the rules mentioned in the preceding paragraph. The most foolproof *chemical* method is that of closing or opening a ring. Thus, if two groups capable of combining are cis oriented, they often can be treated so as to close a ring, but not if the orientation is trans; e.g.,





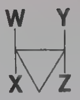
Similarly, if only one isomer can be prepared by a ring opening, it is the cis isomer. For example, only maleic and not fumaric acid may be prepared by oxidation of benzene (reaction **9-11**, p. 875). Other chemical methods of distinguishing cis from trans isomers involve correlation with known compounds, and reaction by routes of known mechanism.

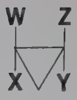
Geometrical Isomerism of Monocyclic Compounds. Although rings of four carbons and larger are not planar (see p. 108), they will be treated as such in this section, since the correct number of isomers can be determined when this is done, and the principles are easier to visualize (see p. 107).

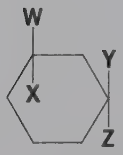
As does a double bond, the presence of a ring prevents rotation, and cis and trans isomers are possible whenever there are two carbons on a ring, each of which is substituted by two different groups. The two carbons need not be adjacent. Examples are

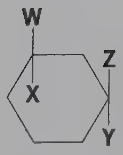
---

[53] For a review of cis-trans isomerism, see Wyman, *Chem. Rev.* **55**, 625–657 (1955).

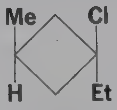








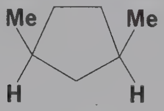
As is the case with double bonds, W may equal Y and X may equal Z, but W may not equal X, and Y may not equal Z, if there is to be geometrical isomerism. There is an important difference from the double-bond case: the substituted carbons are asymmetric. This means that there are not *only* two isomers. In the most general case, where W $\neq$ X $\neq$ Y $\neq$ Z, there are four isomers, since neither the cis nor the trans isomer is superimposable on its mirror image. This is true regardless of ring size, or of which carbons are involved, except that in rings of even-numbered size, when the asymmetric carbons are opposite each other, no optical activity is present, e.g., in **33.** Note that a plane of symmetry exists in such compounds. When W = Y and X = Z,



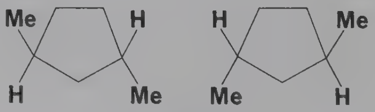
meso

33

then the cis isomer is always superimposable on its mirror image and hence is a meso compound, while the trans isomer consists of a *dl* pair, except in the case noted above:

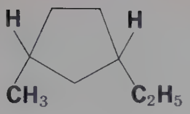


cis meso

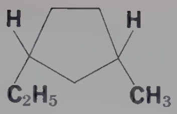


trans *dl* pair

Again, the cis isomer has a plane of symmetry, while the trans does not. In cyclic compounds the line between optical and geometrical isomerism becomes exceedingly thin. Everyone would agree that the pair **34** and **35** represents a case of optical isomerism, but are **35** and **36** optical isomers (diastereomers) or geometrical isomers? This example illustrates that these categories are not mutually exclusive. The ambiguity may be cleared up by defining diastereomers as *any stereoisomers which are not enantiomers,* rather than the more restrictive classical definition given on page 87, and this definition has been adopted by many workers. Note that under this definition all geometrical isomers are diastereomers.

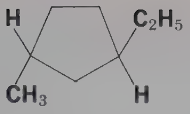


34

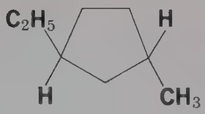


35

cis *dl* pair



36



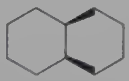
37

trans *dl* pair

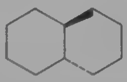
Rings with more than two differently substituted carbons may be dealt with on similar principles. In some cases it is not easy to tell by inspection just how many isomers there are. The best method for the student is to count the number n of differently substituted carbons (these will normally be asymmetric, but not always, e.g., in **33**) and then draw 2^n structures, crossing out those which can be superimposed on others (usually the easiest method is to look for a plane of symmetry). By this means it may be determined that for 1,2,3-cyclohexanetriol there are two meso compounds and a *dl* pair; and for 1,2,3,4,5,6-hexachlorocyclohexane there are seven meso compounds and a *dl* pair. The drawing of these structures is left as an exercise for the student.

Similar principles apply to heterocyclic rings, as long as there are carbons (or other ring atoms) containing two different groups.

Geometrical Isomerism of Fused-ring Systems. Where the rings are fused through adjacent atoms, there is no new principle. The fusion may be cis or trans, as illustrated by *cis*- and *trans*-decalin:

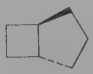


cis-Decalin

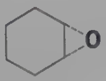


trans-Decalin

However, when the rings are small enough, the trans configuration is impossible, and the junction must be cis. The smallest trans junction which has been prepared when one ring is four-membered is a four-five junction: *trans*-bicyclo[3.2.0]heptane is known.[54]



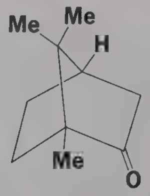
For the bicyclo[2.2.0] system (a four-four fusion) only cis compounds have been made. Trans junctions are also unknown when one ring is three-membered and the other six-membered or smaller; e.g., only *cis*-cyclohexene oxide is known.



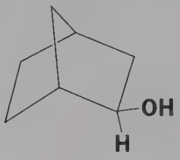
---

[54] Meinwald, Tufariello, and Hurst, *J. Org. Chem.* **29**, 2914 (1964).

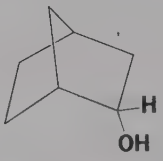
Rings which are fused through nonadjacent atoms are called *bridged.* In bridged-ring systems there may be fewer than 2^n isomers because of the structure of the system. For example, there are only two isomers of camphor (**38**) (a *dl* pair) although it has two asymmetric carbons. In both isomers the methyl and hydrogen are cis. The trans pair of enantiomers is impossible in this case, since the bridge *must* be cis. In substituted bridged bicyclic systems, that isomer which has the group on the same side as the bridge is called *exo,* while the other is *endo.*



38

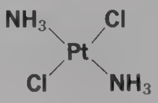


exo-2-Norborneol

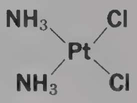


endo-2-Norborneol

Inorganic Geometrical Isomerism.[55] There are several types of geometrical isomerism in inorganic compounds; we shall mention only two. In coordination compounds whose geometry is square planar, cis and trans isomerism may exist, as in this example:

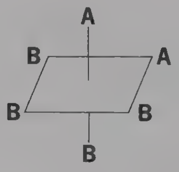


trans

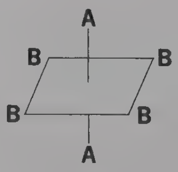


cis

In octahedral coordination compounds of the type MA_2B_4, cis-trans isomerism also exists:



cis

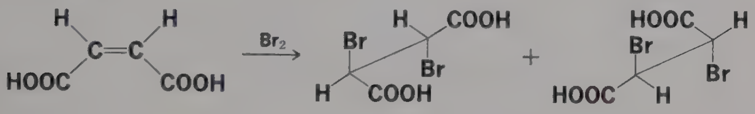


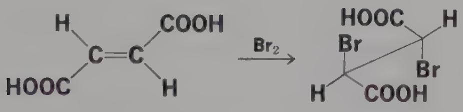
trans

---

[55] For a review, see Gillespie and Nyholm, *Quart. Rev.* (*London*) **11**, 339–380 (1957).

Stereospecific and Stereoselective Syntheses. Any reaction in which only one of a set of stereoisomers is formed exclusively or predominantly is called a *stereoselective* synthesis.[56] The same term is used when a mixture of two or more stereoisomers is exclusively or predominantly formed at the expense of other stereoisomers. In a *stereospecific* reaction, a given isomer leads to one product, while another stereoisomer leads to the opposite product. All stereospecific reactions are necessarily stereoselective, but the converse is not true. These terms are best illustrated by examples. Thus, if maleic acid, treated with bromine, gives the *dl* pair of 2,3-dibromosuccinic acid, while fumaric acid gives the meso isomer (this is the case), the reaction is stereospecific as well as stereoselective, because two opposite isomers give two opposite isomers:





However, if both maleic and fumaric acid gave the *dl* pair, or a mixture in which the *dl* pair predominated, the reaction would be stereoselective, but not stereospecific. If more or less equal amounts of *dl* and meso forms were produced in each case, the reaction would be nonstereoselective. A consequence of these definitions is that, if a reaction is carried out on a compound which has no stereoisomers, it cannot be stereospecific, but at most stereoselective. For example, addition of bromine to methylacetylene could (and does) result in preferential formation of *trans*-1,2-dibromopropene, but this can be only a stereoselective and not a stereospecific reaction. Unfortunately, the term stereospecific is sometimes used in the literature where stereoselective is meant.

CONFORMATIONAL ANALYSIS

If two different three-dimensional arrangements in space of the atoms in a molecule are interconvertible merely by free rotation about bonds, they are called *conformations;* if not, *configurations.*[57] Configurations represent *iso-*

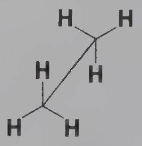
---

[56] For a further discussion of these terms, and of stereoselective reactions in general, see Eliel, Ref. 1, pp. 434–446.

[57] For treatises on conformational analysis, see Eliel, Allinger, Angyal, and Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, 1965; and Hanack, "Conformation Theory," Academic Press Inc., New York, 1965. For reviews, see Barton and Cookson, *Quart. Rev.* (*London*) **10,** 44–82 (1956); Dauben and Pitzer, in Newman, "Steric Effects in Organic Chemistry," pp. 1–60, John Wiley & Sons, Inc., New York, 1956; and Lau, *Angew. Chem.* **73,** 423–432 (1961).

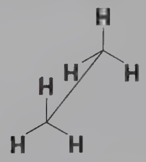
mers which can be separated, as previously discussed in this chapter. Conformations represent *conformers,* which are rapidly interconvertible and thus nonseparable. The term "conformational isomer" (unfortunately, sometimes, just "isomer") is often used instead of "conformer."

Conformation in Open-chain Systems. In an open-chain system there are an infinite number of conformations possible, each of which has a certain energy associated with it. For ethane there are two extremes, a conformation of highest and one of lowest potential energy, depicted in **39** and **40**, and, by another type of diagram, in **41** and **42**. In the latter type of diagram, called the *Newman projection formula,* the observer is looking at the C—C bond head on. The three lines emanating from the center of the circle represent the valences of the front carbon, with respect to the observer.



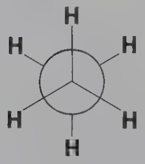
39

staggered



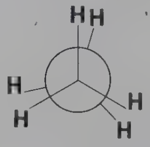
40

eclipsed



41

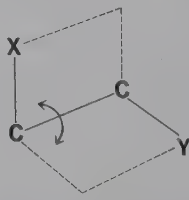
staggered



42

eclipsed

The staggered conformation (**39** or **41**) is the conformation of lowest potential energy for ethane. As the bond rotates, the energy gradually increases until the eclipsed conformation (**40** or **42**) is reached, when the energy is at a maximum. Further rotation decreases the energy again. Figure 3 illustrates this. The *angle of torsion,* also called the *dihedral angle,* is the angle between the X—C—C and the C—C—Y planes, as shown:



For the case of ethane, the difference in energy is about 2.8 kcal/mole.[58] This difference is called the *energy barrier,* since in free rotation about

---

[58] Lide, *J. Chem. Phys.* **29**, 1426 (1958).

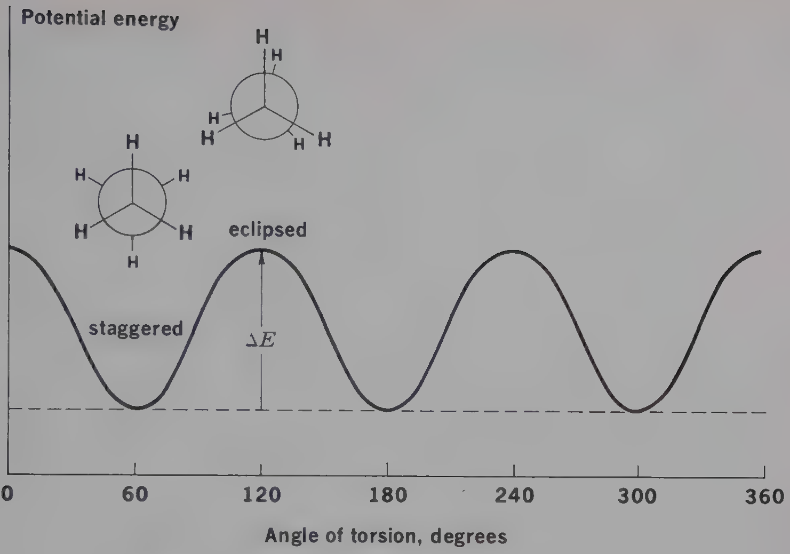


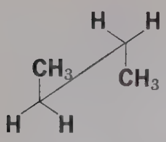
Figure 3. *Conformational energy diagram for ethane.*

a single bond there must be enough rotational energy present to cross the barrier every time two hydrogen atoms are opposite each other. The cause of such barriers is not yet known.[59] At ordinary temperatures there is enough rotational energy present so that the ethane molecule is rapidly rotating, though it still spends most of its time at or near the energy minimum. Groups larger than hydrogen cause larger barriers, and when the barriers are large enough, as in the case of suitably substituted biphenyls (p. 76), rotation at room temperature is completely prevented, and we may speak of configurations and not conformations. Even for compounds with small barriers, cooling to low temperatures may remove enough rotational energy so that what would otherwise be conformational isomers become configurational isomers. Isomers which can be separated only because rotation about single bonds is prevented or greatly slowed are called *atropisomers.*

A case slightly more complicated than that of ethane is that of a 1,2-disubstituted ethane, such as *n*-butane. In this case there are four extremes: a fully staggered conformation, called *anti,* or *trans* (**43**) (lowest energy); a *skew,* or *gauche,* conformation (**45**); and two types of eclipsed conformations (**44** and **46**). An energy diagram for this system is given in Figure 4. Although there is constant rotation about the central bond, it is possible to estimate what percentage of the molecules are in each conformation at a given time. For example, for 1,2-dichloroethane, in CCl_4 solution at 25°,

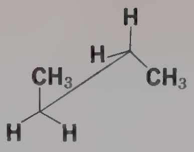
---

[59] For a review of methods of measuring barriers and of values of barriers, see Millen, *Progr. Stereochem.* **3,** 138–168 (1962). For a review of attempts to explain barriers, see Wilson, *Advan. Chem. Phys.* **2,** 367–393 (1959). Of course, it may be that one of the explanations already offered is correct and merely awaits confirmation. For recent explanations, see Scott and Scheraga, *J. Chem. Phys.* **42,** 2209 (1965); Wyatt and Parr, *J. Chem. Phys.* **43,** S217 (1965), **44,** 1529 (1966); and Lowe and Parr, *J. Chem. Phys.* **43,** 2565 (1965), **44,** 3001 (1966).



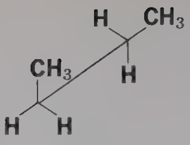
anti,
or
trans

43



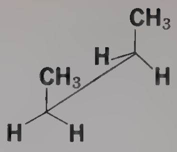
partly
eclipsed

44



gauche, or
skew

45



fully
eclipsed

46

about 70% of the molecules are in the anti, and about 30% in the gauche conformation.[60] The corresponding figures for 1,2-dibromoethane are 89% anti and 11% gauche. The eclipsed conformations are unpopulated and serve only as pathways from one staggered conformation to another. Solids normally consist of a single conformer.

It may be observed that the gauche conformation of butane (**45**) or of any other similar molecule is nonsuperimposable on its mirror image. The lack of optical activity in such compounds arises from the facts that **45** and its mirror image are always present in equal amounts and that they interconvert too rapidly for separation.

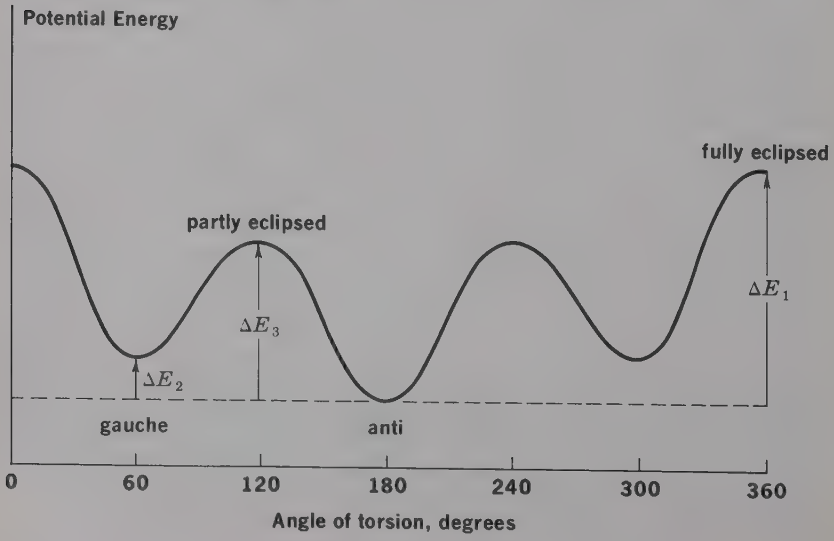
Conformation in Six-membered Rings.[61] If the six carbons of cyclohexane were to lie in a plane, the bond angles would have to be 120°, since these are

---

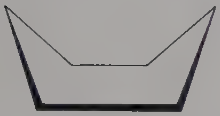
[60] Aroney, Izsak, and Le Fèvre, *J. Chem. Soc.* **1962,** 1407; Le Fèvre and Orr, *Australian J. Chem.* **17,** 1098 (1964).

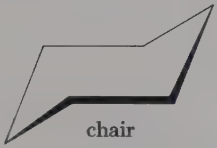
[61] For reviews, see Klyne, *Progr. Stereochem.* **1,** 36–89 (1954); Hassel, *Quart. Rev.* (*London*) **7,** 221–230 (1953); Orloff, *Chem. Rev.* **54,** 348–447 (1954); Eliel, *Angew. Chem. Intern. Ed. Engl.* **4,** 761–774 (1965).

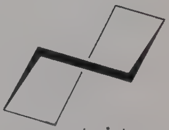
Figure 4. *Conformational energy for* $YCH_2—CH_2Y$. *For n-butane,* $\Delta E_1 = 4\text{-}6$; $\Delta E_2 = 0.8$; *and* $\Delta E_3 = 3.4$ *kcal/mole.*

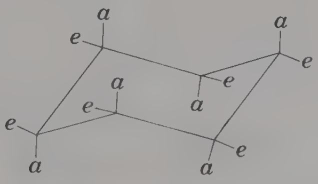


the angles of a regular hexagon. Since the normal tetrahedral angle is about 109.5°, there would be strain. The existence of cyclopropane proves that molecules may contain a good deal more strain than this. However, cyclopropane *must* be planar—there is no other conformation possible—whereas for cyclohexane there are two extreme conformations in which all the angles are tetrahedral.[62] These are called the *boat* and the *chair* conformations, and in each the ring is said to be *puckered*. The boat is an eclipsed form, corresponding to an energy maximum (see p. 119). The *twist* conformation, also called the *flexible*, the *skew boat*, or even the *nonchair* form, represents an energy minimum whose energy is about 1.5 kcal/mole less than that of the boat form. The chair form is more stable than the twist form by about 5 kcal/mole.[63] In the vast majority of compounds containing a cyclohexane ring, the molecules exist almost entirely in the chair form. Yet it is known that the twist form exists transiently. An inspection of the chair form shows that six of its bonds are directed in a manner different from the other six:


boat


chair


twist



On each carbon one bond is directed up or down, and the other, more or less in the "plane" of the ring. The up or down bonds are called *axial* and the others *equatorial*. The axial bonds point alternately up and down. If a molecule were frozen into a chair form, then there would be isomerism in monosubstituted cyclohexanes. For example, there would be an equatorial methylcyclohexane and an axial isomer. However, it has never been possible to isolate isomers of this type at room temperature. This proves the transient existence of the twist form, since in order for the two types of methylcyclohexane to be nonseparable, there must be rapid interconversion of one chair form to another (in which all axial bonds become equatorial and vice versa), and this is possible only through a twist conformation. Conversion of one chair form to another requires an activation energy of about 10 kcal/mole[64] and is thus very rapid at room temperature. However, by working at low temperatures, Jensen and Bushweller have been able to obtain the pure equatorial conformers of chlorocyclohexane and trideuteriomethoxycyclohexane, as solids and in solution.[64a]

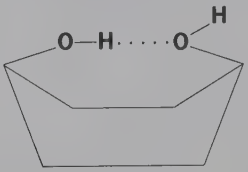
---

[62] The C—C—C angles in cyclohexane are actually 111.5° [Davis and Hassel, *Acta Chem. Scand.* **17**, 1181 (1963)], but this is within the normal tetrahedral range (see p. 24).

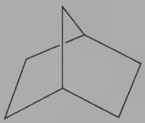
[63] Margrave, Frisch, Bautista, Clarke, and Johnson, *J. Am. Chem. Soc.* **85**, 546 (1963).

[64] Jensen, Noyce, Sederholm, and Berlin, *J. Am. Chem. Soc.* **84**, 386 (1962); Anet, Ahmad, and Hall, *Proc. Chem. Soc.* **1964**, 145; Bovey, Hood, Anderson, and Kornegay, *J. Chem. Phys.* **41**, 2041 (1964).

In some molecules the twist conformation is actually preferred.[65] An example is **47**, in which hydrogen bonding stabilizes the otherwise high energy form. Of course, in certain bicyclic compounds the six-membered ring is forced to maintain a boat conformation, as in norbornane (**48**).



47



48

In monosubstituted cyclohexanes, the substituent normally prefers the equatorial position, although the extent of this preference is greatly dependent on the nature of the group. Alkyl groups have a greater preference than polar groups, and for alkyl groups the preference increases with size. For polar groups, size seems to be unimportant. Both the large HgBr group[66] and the small F group have been reported to have little or no conformational preference. Table 2 gives values of the free energy required for various groups to go from the equatorial position to the axial.[67]

In disubstituted compounds, the rule for nonpolar groups is: the conformation will be such that as many groups as possible adopt the equatorial position. How far it is possible depends on the configuration. In a *cis*-1,2-disubstituted cyclohexane, one substituent must be axial and the other equatorial. In a *trans*-1,2 compound both may be equatorial or both axial. This is also true for 1,4-disubstituted cyclohexanes, but for 1,3 compounds, the reverse holds: the trans isomer must have the *ae* conformation, and the cis isomer may be *aa* or *ee*. For alkyl groups, the diequatorial conformation predominates over the diaxial, but for other groups this is not necessarily so. For example, both *trans*-1,4-dibromocyclohexane and the corresponding dichloro compound have the *ee* and *aa* conformations about equally populated.[68] Since compounds with equatorial substituents are generally more stable, *trans*-1,2 compounds, which can adopt the *ee* conformation, are thermodynamically more stable than their *cis*-1,2 isomers, which must exist in the *ae* conformation. For the 1,2-dimethylcyclohexanes, the difference in stability is about 2 kcal/mole. Similarly, *trans*-1,4 and *cis*-1,3 compounds are more stable than their stereoisomers.

[64a] Jensen and Bushweller, *J. Am. Chem. Soc.* **88,** 4279 (1966).

[65] Stolow, *J. Am. Chem. Soc.* **83,** 2592 (1961); Stolow and Boyce, *J. Am. Chem. Soc.* **83,** 3722 (1961); Lautenschlaeger and Wright, *Can. J. Chem.* **41,** 1972 (1963). For a review of nonchair forms, see Balasubramanian, *Chem. Rev.* **62,** 591 (1962).

[66] Jensen and Gale, *J. Am. Chem. Soc.* **81,** 6337 (1959).

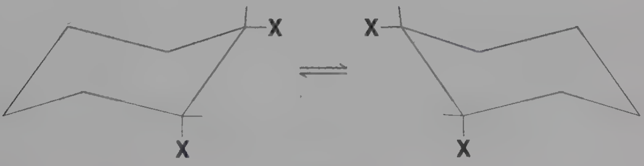
[67] For an extensive discussion of conformational preferences in mono-, di-, and polysubstituted cyclohexanes, see Hanack, Ref. 57, pp. 89–142.

[68] Atkinson and Hassel, *Acta Chem. Scand.* **13,** 1737 (1959).

TABLE 2. Free-energy differences between equatorial and axial substituents[69] The values (in kilocalories per mole) are approximate. For NH_2 and OH, the lower values apply to aprotic and the higher to protic solvents (see p. 295)

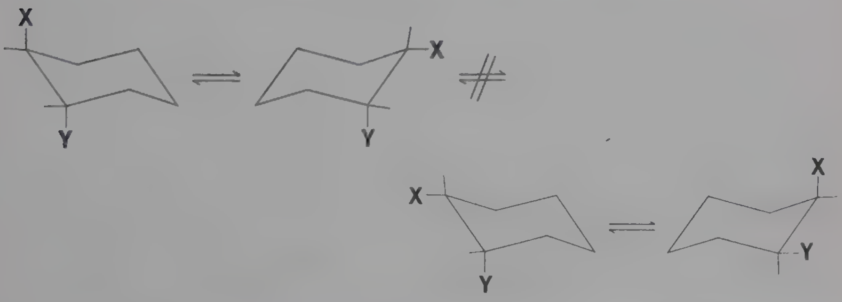
Group	$-\Delta G^0$	*Group*	$-\Delta G^0$
HgBr	0	OEt	0.9
F	0.2	SH	0.9
C≡CH	0.2	COOMe	1.1
CN	0.2	COOH	1.2
Cl	0.4	NH_2	1.2–1.8
Br	0.4	CH_3	1.7
I	0.4	C_2H_5	1.8
OH	0.6–0.9	*iso*-Pr	2.1
OAc	0.7	C_6H_{11}	2.2
OTs	0.7	C_6H_5	3.1
OMe	0.7	*tert*-Bu	>4.4

Incidentally, we may now see, in one case, why the correct number of stereoisomers could be predicted by assuming planar rings, even though they are not planar (p. 97). In the case of both a *cis*-1,2-XX-disubstituted and a *cis*-1,2-XY-disubstituted cyclohexane, the molecule is nonsuperimposable on its mirror image; neither has a plane of symmetry. However, in the former case:



49

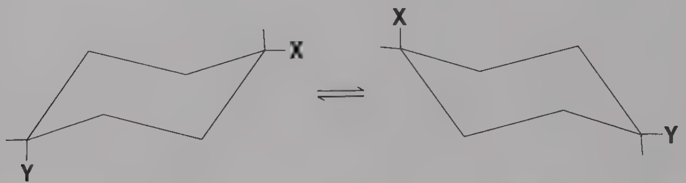
conversion of one chair form to the other (which of course happens rapidly) turns the molecule into its mirror image, while in the latter case:



---

[69] These values are from Eliel, Ref. 61, p. 764. See also the tables in Eliel, Allinger, Angyal, and Morrison, Ref. 57, pp. 44, 436–442.

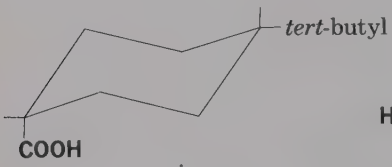
rapid interconversion does not give the mirror image, but merely the conformer in which the original axial and equatorial substituents exchange places. Thus the optical inactivity of **49** is not due to a plane of symmetry, but to a rapid interconversion of the molecule and its mirror image. A similar situation obtains for *cis*-1,3 compounds. However, for *cis*-1,4 isomers (both XX and XY) optical inactivity arises from a plane of symmetry in both conformations:



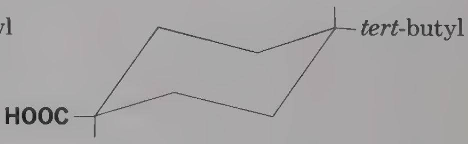
Symmetric Symmetric

All *trans*-1,2- and -1,3-disubstituted cyclohexanes are optically active (whether XX or XY), while *trans*-1,4 compounds (both XX and XY) are optically inactive, since all conformations have a plane of symmetry.

The conformation of a group may be "frozen" into a desired position by putting into the ring a large alkyl group (most often *tert*-butyl), which must adopt the equatorial position.[70] For example, it was desired to compare the acidity of the carboxyl group in the axial and in the equatorial position. For this purpose the *cis*- and *trans*-4-*tert*-butylcyclohexanecarboxylic acids were synthesized. The geometry is such that in the cis compound the equatorial *tert*-butyl group forces the carboxyl group to be axial, while in the trans compound it must be equatorial:



cis; *ae*



trans; *ee*

The equatorial COOH had the greater acidity.[71]

The principles involved in the conformational analysis of other six-membered rings (e.g., containing trigonal or hetero atoms, such as cyclohexene, cyclohexanone, or piperidine) are similar (see Refs. 57 and 61).

Conformation in Other Rings. Three-membered rings must be planar, but they seem to be the only saturated rings which generally are. Cyclobutane is not planar but exists as in **50**,[72] with an angle between the planes of about

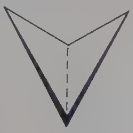
---

[70] This idea was suggested by Winstein and Holness, *J. Am. Chem. Soc.* **77,** 5562 (1955).

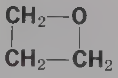
[71] Stolow, *J. Am. Chem. Soc.* **59,** 5806 (1959).

[72] Almenningen, Bastiansen, and Skancke, *Acta Chem. Scand.* **15,** 711 (1961); Lambert and Roberts, *J. Am. Chem. Soc.* **87,** 3884, 3891 (1965). However, some cyclobutane derivatives are planar; for example, see Margulis and Fischer, *J. Am. Chem. Soc.* **89,** 223 (1967).

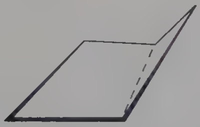
20°. The deviation from planarity is presumably caused by eclipsing in the planar form (see p. 119). Oxetane (**51**), in which eclipsing is less, is apparently planar.[73] Cyclopentane might be expected to be planar, since the angles of a regular pentagon are 108°, but it is not so, also because of eclipsing effects. There are two puckered conformations, the *envelope* and the *half-chair:*



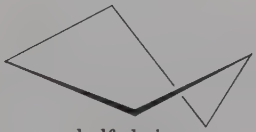
50



51



envelope



half-chair

Although in the envelope conformation one carbon is shown above the others, ring motions cause each of the carbons, in rapid succession, to assume this position. The puckering rotates around the ring in what may be called a *pseudorotation.*[74] In substituted cyclopentanes, and in five-membered rings in which at least one atom does not contain two substituents (such as tetrahydrofuran, cyclopentanone, etc.), one conformer may be more stable than the others. Thus the preferred conformation for methylcyclopentane is the envelope, with the carbon containing the methyl group above the plane of the other four carbons.

Rings larger than six-membered are always puckered,[75] unless they contain a large number of sp^2 atoms (see the section on strain in medium rings, p. 119).

Methods for Determining Conformations.[76] X-ray- and electron-diffraction techniques, which are capable of measuring bond distances and angles, obviously can give conformations too. X-ray diffraction, which can be used only on solids, has been more successful in this respect, because all of the molecules in a crystal have the same conformation. However, this very virtue is also a drawback, because the conformation of the solid is not necessarily the same as that of the molecules in other phases. Dipole moments

---

[73] Chan, Zinn, Fernandez, and Gwinn, *J. Chem. Phys.* **33,** 1643 (1960).

[74] Kilpatrick, Pitzer, and Spitzer, *J. Am. Chem. Soc.* **69,** 2438 (1947); Pitzer and Donath, *J. Am. Chem. Soc.* **81,** 3213 (1959).

[75] For reviews of conformations in larger rings, see Dale, *Angew. Chem. Intern. Ed. Engl.* **5,** 1000–1021 (1966); Dunitz and Prelog, *Angew. Chem.* **72,** 896–902 (1960); Prelog, *Pure Appl. Chem.* **6,** 545–560 (1963); and Sicher, *Progr. Stereochem.* **3,** 202–264 (1962). Also see the monographs by Hanack and by Eliel, Allinger, Angyal, and Morrison, Ref. 57.

[76] For reviews, see Lau, *Angew. Chem.* **73,** 423–432 (1961); Klyne, *Progr. Stereochem.* **1,** 36–89 (1954); and Eliel, Allinger, Angyal, and Morrison, Ref. 57, pp. 129–188.

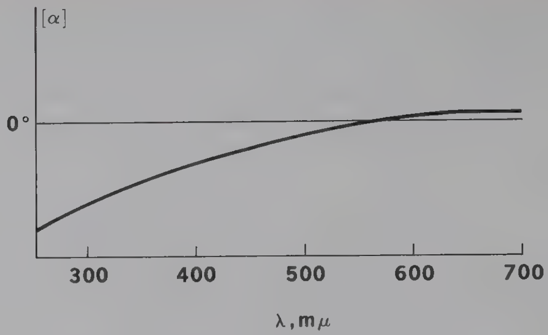


Figure 5. *A plain curve.*

can often be used to determine conformations. For example, 1,2-dibromoethane should have no dipole moment in the anti conformation but should have a moment in the gauche conformation. Since the compound has a dipole moment of 0.93 D, it must exist at least partially in the gauche form. A consideration of dipole moments and polarizabilities led to the conclusion that 89% of the molecules are in the anti and 11% in the gauche conformations.[60] Conformations have also been determined from infrared, Raman, ultraviolet, nuclear magnetic resonance, and microwave spectra (see Chapter 6).

A method of determining conformation when the absolute configuration is known depends on measuring the *optical rotatory dispersion* (ord).[77] It has been mentioned that, when a dissymmetric compound rotates the plane of polarized light, the amount of rotation depends on the wavelength of the polarized light. In optical rotatory dispersion, rotations are measured over a range of wavelengths rather than at a single wavelength, usually covering the ultraviolet as well as the visible region. Instruments which do this and plot the rotation as a continuous function of the wavelength are commercially available. Some compounds give what is called a *plain curve* (Figure 5), while others illustrate the *Cotton effect* (Figure 6). In a *positive* Cotton effect, as the wavelength decreases, the rotation takes a fairly sharp increase, reaches a peak, and then precipitously sinks to a trough, after which it rises again. The descending line always crosses the zero axis at a wavelength at which the compound absorbs light (see Chapter 6), though not all such wavelengths show the Cotton effect. A *negative* Cotton effect is the reverse:

---

[77] For monographs, see Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Company, New York, 1960; and Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, 1965. For reviews, see Eliel, Ref. 1, pp. 412–433; Klyne, *Advan. Org. Chem.* **1,** 239–348 (1960); Djerassi, *Pure Appl. Chem.* **2,** 475–504 (1961), *Proc. Chem. Soc.* **1964,** 314; Yufit and Kucherov, *Russ. Chem. Rev.* **31,** 235–244 (1962); Klyne and Parker, in Weissberger, "Technique of Organic Chemistry," vol. 1, part 3, 3d ed., pp. 2335–2385, Interscience Publishers, Inc., New York, 1960; and Lyle and Lyle, in Nachod and Phillips, "Determination of Organic Structures by Physical Methods," vol. 2, pp. 1–92, Academic Press Inc., New York, 1962. For a symposium, see *Tetrahedron* **13,** 1–240 (1961).

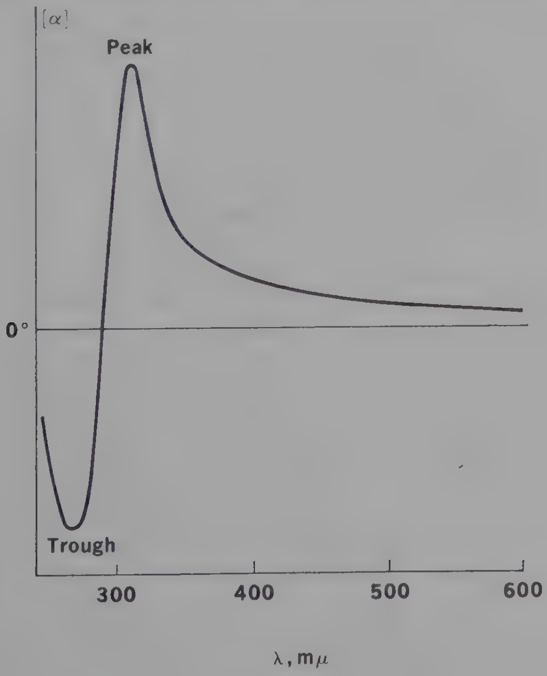
as the wavelength decreases, there is first a drop and then a sharp rise. Obviously, if any compound shows a positive Cotton effect, its enantiomer must show a negative one.

Plain curves are much less useful than curves which show a Cotton effect, but sometimes a comparison of the plain curves of two similar compounds can show the absolute configuration of one if the configuration of the other is known. Another use for plain curves is in the detection of optical activity when a measurement at the usual wavelength (589 mμ, corresponding to the D line of Na) does not indicate activity. In some cases the rotation of 589 mμ is so low that it is undetectable, but it is usually greater in the ultraviolet region.

Curves which exhibit Cotton effects have been much more useful, yielding information on structure, configuration, and conformation, though the relationships are largely empirical. The basic method is one of comparison of the peaks of unknown with those of known compounds. Although much useful work has been carried out on other compounds, up to now the bulk of ord studies have been performed on cyclic ketones. The keto group absorbs in the ultraviolet at about 280 to 290 mμ, and this absorption generally gives rise to a Cotton effect. Cyclic compounds are more rigid than acyclic ones and thus more amenable to conformational study.

An illustration of the type of correlations made possible by a comparison

Figure 6. *An optical rotatory dispersion curve showing a positive Cotton effect.*



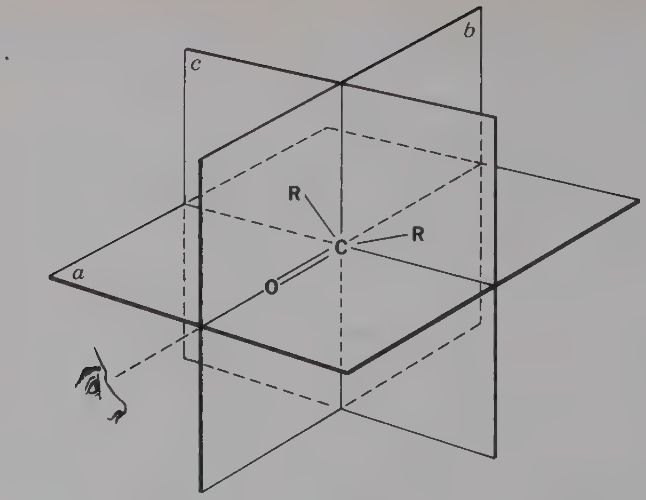
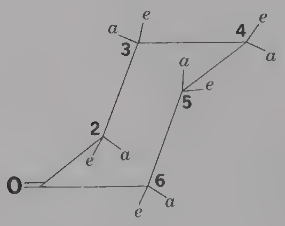
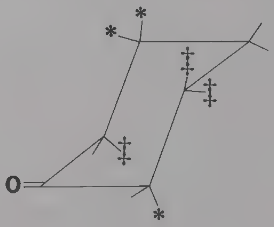


Figure 7. *The three perpendicular planes of the octant rule.*

of Cotton-effect curves may be obtained by a consideration of the *octant rule.*[78] According to this rule, a carbonyl compound is cut into octants by three perpendicular planes which meet at the carbonyl carbon (Figure 7). For a six-membered ring (**52**) one plane is the plane which includes C-1, C-2, C-6, and the carbonyl oxygen. In the diagram shown, this plane lies below C-3, C-4, and C-5. The second plane is perpendicular to the first, includes C-1, C-4, and the oxygen, and bisects the ring. In the diagram, C-2 and C-3 lie behind this plane, and C-5 and C-6 in front of it. The third plane includes C-1 and is perpendicular to the other two. In **52** only the oxygen lies to the left of the third plane; all other atoms lie to the right. The three planes cut the molecule into eight sections, four of which, in this case, are unoccupied by atoms. The octant rule may then be stated for the four octants which are occupied in **52.** Substituents which are *in the planes* (unmarked in **53**) have little or no effect on the ord curve; substituents in



52



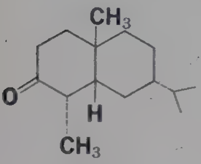
53

---

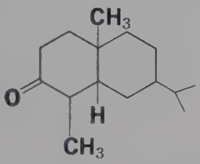
[78] Moffitt, Woodward, Moscowitz, Klyne, and Djerassi, *J. Am. Chem. Soc.* **83,** 4013 (1961); Djerassi and Klyne, *J. Chem. Soc.* **1962,** 4929.

the lower-right and upper-left octants (marked *) make a positive contribution to the Cotton-effect curve; and substituents in the upper right and lower left octants (marked ‡) make a negative contribution. For the other four octants (these are occupied in some compounds with fused ring systems) the contributions are reversed.[79]

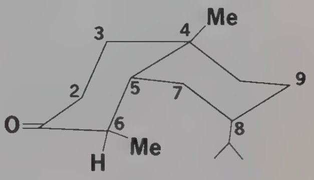
An example of the use of ord to establish conformation may be seen in the case of the *cis*-tetrahydrocyperones, the absolute configurations of which are known and are shown in **54** and **55:**



54



55



56

The question in each case is: is the isopropyl group axial or equatorial? If **54** has an axial isopropyl group, it has the configuration shown in **56.** If we number the ketone ring as in **52,** we see that the C-4 methyl group makes no contribution, but that the isopropyl group projects into the lower-right octant and thus makes a positive contribution, as does the C-6 methyl. A look at the model (Figure 8*a*) shows that the positive contributions outweigh the negative, and **56** should show a positive, though weak, Cotton effect. Similarly, a photograph of the conformation which would result if the isopropyl group in **54** were equatorial (Figure 8*b*) shows that this conformer should exhibit a strong positive Cotton effect. The actual ord curve for **54** showed a strong positive Cotton effect, indicating that **54** has the conformation shown in Figure 8*b*, with an equatorial isopropyl group. Similarly, **55** exhibited a weak negative Cotton effect,[80] showing that in this isomer too the isopropyl group is equatorial (Figure 8*c*). If the isopropyl group had been axial, the Cotton effect would have been strongly positive (Figure 8*d*).

If the conformation is known, ord may be used to establish configuration. This is done by comparison of the ord curve of the compound of unknown configuration with that of a substance of known configuration, providing that the two compounds contain the same light-absorbing group in the same environment. For example, a comparison of the ord curve of friedelin (**57**) with those of the known compounds **58** and **59** (which differ only in configuration at C-18) shows that **57** and **59** have almost identical curves, while that of **58** is much shallower. Although the configuration at C-4 of friedelin was already known, ord provided confirmatory evidence.[81]

In many cases, compounds may be made more amenable to ord study by

---

[79] Ethylene oxide (oxiran) and cyclopropane rings make *opposite* contributions: Djerassi, Klyne, Norin, Ohloff, and Klein, *Tetrahedron* **21**, 163 (1965).

[80] Djerassi, "Optical Rotatory Dispersion," p. 186, McGraw-Hill Book Company, New York, 1960.

[81] Djerassi, Riniker, and Riniker, *J. Am. Chem. Soc.* **78,** 6362 (1956).

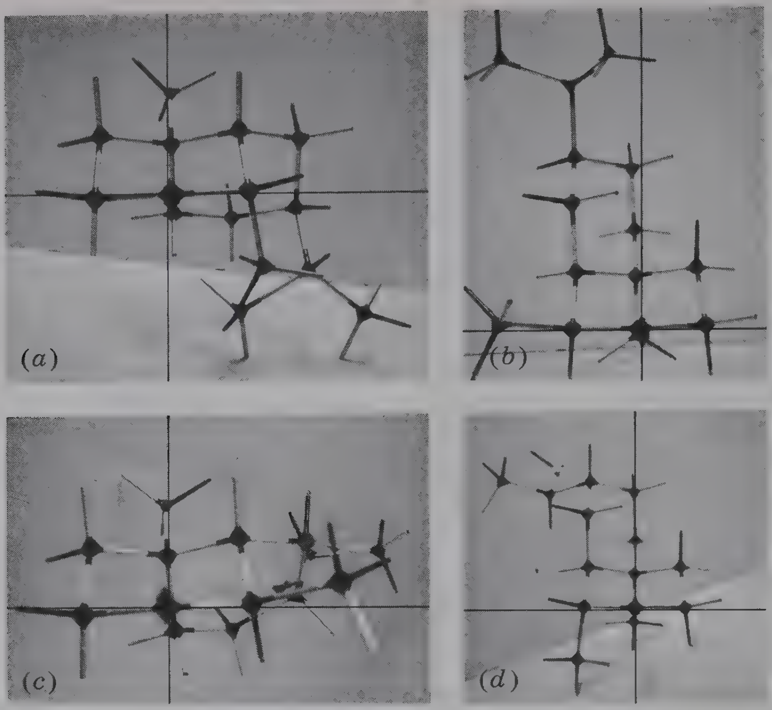
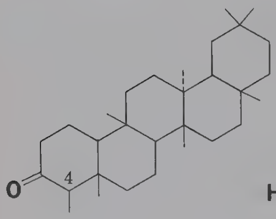
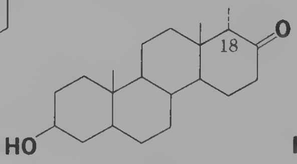


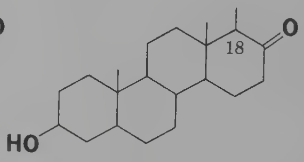
Figure 8. *Photographs of models of the cis-tetrahydrocyperones. (a)* **54** *in the conformation in which the isopropyl group is axial; (b)* **54** *in the conformation in which the isopropyl group is equatorial; (c)* **55** *in the conformation in which the isopropyl group is equatorial; (d)* **55** *in the conformation in which the isopropyl group is axial.*



57



58



59

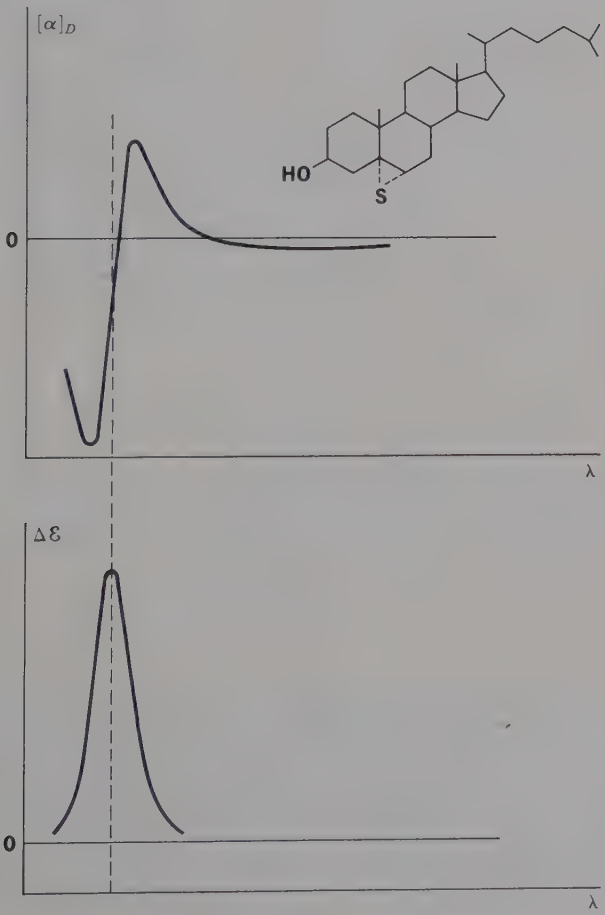
conversion of a group which does not absorb in the visible to one that does (if this change does not affect the stereochemistry). For example, the OH group may be converted to the ONO group.

A technique closely related to ord is *circular dichroism* (cd).[82] In this method the molecular extinction coefficients (p. 170) of a compound are measured with both left and right circularly polarized light, and the difference between these values (called Δε) is plotted against the wavelength of the light used. Instruments are available which automatically plot Δε against λ in the visible and ultraviolet regions of the spectrum. As with ord, information is obtained chiefly in regions where the molecule absorbs light. Circular dichroism curves are typically bell-shaped, with a maximum or a minimum at the absorption peak. In Figure 9 are compared an ord curve and a cd curve for the same compound. As illustrated in Figure 9, a positive Cotton effect is associated with a positive Δε. Of course, the enantiomer of the compound illustrated in Figure 9 would have a negative Cotton effect and a negative Δε. As with ord, interpretation of cd curves is largely empirical, and information is obtained by comparison of curves of known and unknown compounds. The octant rule also applies to cd, and it is used to determine

---

[82] For monographs, see Velluz, Legrand, and Grosjean, "Optical Circular Dichroism," Academic Press Inc., New York, 1965; and Crabbé, Ref. 77.

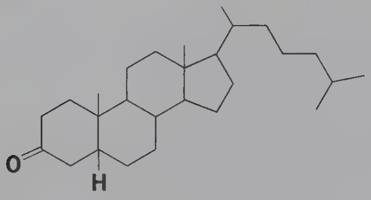
Figure 9. *Optical rotatory dispersion curve (top) and circular dichroism curve (bottom) for 3β-hydroxycholestan-5α,6α-episulfide.*[83]



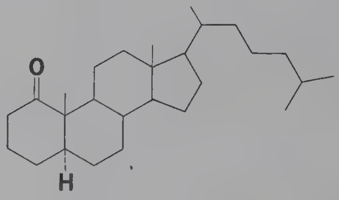
[83] From Djerassi, *Proc. Chem. Soc.* **1964,** 315.

conformations and configurations, in ways similar to those described for ord.[84] In general, the method is limited to approximately the same types of compounds, and most cd work has been done on cyclic ketones.

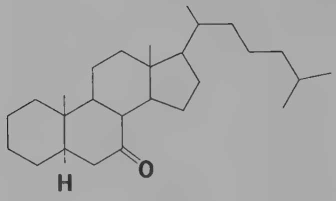
In many cases either ord or cd can be used with equal success to solve the same types of structural and configurational problems. However, cd has the advantage that the curves are generally simpler and easier to interpret. This is largely due to the fact that each absorption peak in a molecule gives rise to a cd peak which is relatively uninfluenced by other parts of the molecule, while an ord peak in a given absorption region is often complicated by background effects from other regions, so that the result is an overlapping of effects. On the other hand, this very complexity often becomes an advantage for ord, since a more complicated curve often yields more information. For example, the cd curves for 3-coprostanone (**60**), 1-cholestanone (**61**), and 7-cholestanone (**62**) are similar, because each is a saturated ketone, but the ord curves are different because of contributions from the rest of the molecule. The two methods are therefore complementary.



60



61



62

STRAIN

Steric strain exists in a molecule when bonds are forced to make angles which are abnormal. This results in a higher energy than would be the case in the absence of angle distortions. There are, in general, two kinds of structural features which result in sterically caused abnormal bond angles. One of these is found in small-ring compounds, where the angles must be less than those resulting from normal orbital overlap. Such strain is called *small-angle strain.* The other arises where nonbonded atoms are forced into close proximity by the geometry of the molecule. These are called *nonbonded interactions.*

---

[84] See Ref. 82 for many examples.

Strain in Small Rings.[85] Three-membered rings have a great deal of angle strain, since 60° angles represent a large departure from the tetrahedral angles. In sharp contrast to other ethers, ethylene oxide is quite reactive, the ring being opened by many reagents (see p. 290). Ring opening, of course, relieves the strain. Cyclopropane,[86] which is even more strained than ethylene oxide, is also cleaved more easily than would be expected for an alkane. Thus, pyrolysis at 450 to 500° converts it to propene, bromination gives 1,3-dibromopropane,[87] and it may be hydrogenated to propane (though at high pressure).[88] Other three-membered rings are similarly reactive.

Molecular-orbital calculations show that the carbon-carbon bonds in cyclopropane are not completely σ in character. In normal C—C bonds, sp^3 orbitals overlap in such a way that the straight line connecting the nuclei becomes an axis about which the electron density is symmetrical. But in cyclopropane, the electron density is directed *away from* the ring. Figure 10 shows the direction of orbital overlap.[89] For cyclopropane, the angle (marked θ) is 21°. Cyclobutane exhibits the same phenomenon, but to a lesser extent, θ being 7°.[89] These bonds are intermediate in character between σ and π, and are called *bent* or *banana bonds* (also see p. 14).

Four-membered rings also exhibit angle strain,[90] but much less, and are less easily opened. Cyclobutane is more resistant to bromination than is cyclopropane, and though it may be hydrogenated to butane, more strenuous conditions are required. Nevertheless, pyrolysis at 420° gives two molecules of ethylene. As mentioned earlier (p. 108), cyclobutane is not planar.

In recent years quite a few highly strained compounds containing fused

---

[85] For a review, see Vogel, *Angew. Chem.* **72**, 4–25 (1960).

[86] For a review on cyclopropanes, see Lukina, *Russ. Chem. Rev.* **31**, 419 (1962).

[87] Ogg and Priest, *J. Am. Chem. Soc.* **60**, 217 (1938).

[88] Shortridge, Craig, Greenlee, Derfer, and Boord, *J. Am. Chem. Soc.* **70**, 946 (1943).

[89] Coulson and Goodwin, *J. Chem. Soc.* **1962**, 2851, **1963**, 3161; Peters, *Tetrahedron* **19**, 1539 (1963).

[90] For a review, see Wilson and Goldhamer, *J. Chem. Educ.* **40**, 504–517 (1963).

Figure 10. *Orbital overlap in cyclopropane. The arrows point toward the center of electron density.*

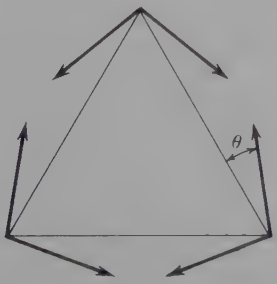
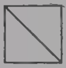
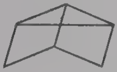
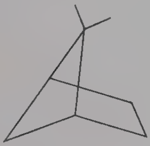
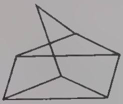
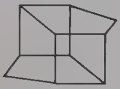
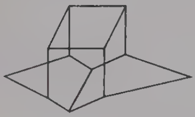
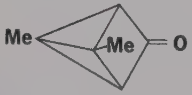
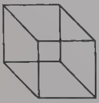
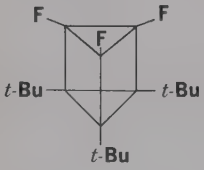
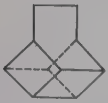


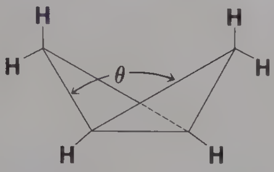
TABLE 3. Some recently prepared strained small-ring systems
For a description of the naming system, see page 924

Structural formula of compound prepared	*Systematic name of ring system*	*Common name if any*	*Ref.*
	Bicyclo[1.1.0]butane	Bicyclobutane	95
	Tricyclo[2.2.0.0^{2,6}]hexane		96
	Bicyclo[2.1.1]hexane		97
	Tetracyclo[2.2.1.0^{2,6}.0^{3,5}]-heptane[91]	Quadricyclene	98
	Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]-decane		99
	Hexacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{4,10}.0^{5,9}]-dodecane	The birdcage hydrocarbon	100
	Tricyclo[1.1.1.0^{2,4}]pentane[91]		101
	Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}] octane	Cubane	102
	Tetracyclo[2.2.0.0^{2,6}.0^{3,5}]hexane	Prismane	103
	Pentacyclo[4.2.2.0^{2,5}.0^{3,8}.0^{4,7}]-decane[91]	Basketane	104

---

[91] These are the names used in the literature. By a strict application of the IUPAC rules, the fourth, seventh, and tenth compounds in Table 3 would be named tetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptane, tricyclo[2.1.0.0^{2,5}]pentane, and pentacyclo[6.2.0.0^{2,7}.0^{3,10}.0^{6,9}]decane, respectively. However, the names given in the table are patterned after those of closely related bicyclic systems.

small rings have been prepared,[92] showing that organic molecules can exhibit much more strain than do simple cyclopropanes or cyclobutanes. Table 3 shows some of these compounds. Perhaps the most interesting are cubane and the prismane derivative, since preparation of these ring systems had been the object of much endeavor. Prismane has the structure which Ladenburg proposed as a possible structure for benzene. The bicyclobutane molecule is bent, with the angle between the planes (θ) equal to 126 ± 3°:[93]



Strain in Medium Rings.[94] In rings larger than four-membered, there is no small-angle strain, but there are three other kinds of strain. First let us examine the chair form of cyclohexane, which does not exhibit any of the three kinds of strain. Each carbon-carbon bond in the chair form may be represented as in **63**; that is, each bond is in the gauche conformation. In five-membered rings, and in rings containing from 7 to 13 carbons, any conformation in which all the bonds are as in **63** contains transannular interactions: interactions between the substituents on C-1 and C-3, or C-1 and C-4, etc. These interactions occur because the internal space is not large enough for all the quasi-axial hydrogen atoms to fit without coming into conflict. The molecule can adopt other conformations in which this *transannular strain* is reduced, but then some of the carbon-carbon bonds must adopt eclipsed

[92] For a review discussing the properties of many of these compounds, see Seebach, *Angew. Chem. Intern. Ed. Engl.* **4,** 121–131 (1965).

[93] Haller and Srinivasan, *J. Chem. Phys.* **41,** 2745 (1964).

[94] For reviews, see Gol'dfarb and Belen'kii, *Russ. Chem. Rev.* **29,** 214–235 (1960); Raphael, *Proc. Chem. Soc.* **1962,** 97–105; and Sicher, *Progr. Stereochem.* **3,** 202–264 (1962).

---

[95] Lemal, Menger, and Clark, *J. Am. Chem. Soc.* **85,** 2529 (1963); Wiberg and Lampman, *Tetrahedron Letters* **1963,** 2173. For reviews of preparations and reactions of this system, see Wiberg, Lampman, Ciula, O'Connor, Schertler, and Lavanish, *Tetrahedron* **21,** 2749–2769 (1965); and Wiberg, *Record Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) **26,** 143–154 (1965).

[96] Lemal and Shim, *J. Am. Chem. Soc.* **86,** 1550 (1964).

[97] Meinwald and Gassman, *J. Am. Chem. Soc.* **82,** 2857 (1960).

[98] Dauben and Cargill, *Tetrahedron* **15,** 197 (1961); Hammond, Turro, and Fischer, *J. Am. Chem. Soc.* **83,** 4647 (1961); Prinzbach and Hartenstein, *Angew. Chem.* **74,** 506 (1962).

[99] McBee, Dilling, and Bracudlin, *J. Org. Chem.* **27,** 2704 (1962).

[100] de Vries and Winstein, *J. Am. Chem. Soc.* **82,** 5363 (1960).

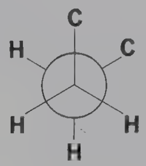
[101] Doering and Pomerantz, *Tetrahedron Letters* **1964,** 961. Also see Masamune, *J. Am. Chem. Soc.* **86,** 735 (1964).

[102] Eaton and Cole, *J. Am. Chem. Soc.* **86,** 3157 (1964); Barborak, Watts, and Pettit, *J. Am. Chem. Soc.* **88,** 1328 (1966).

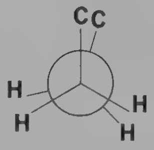
[103] Viehe, Merényi, Oth, Senders, and Valange, *Angew. Chem. Intern. Ed. Engl.* **3,** 755 (1964). See also Lemal and Lokensgard, *J. Am. Chem. Soc.* **88,** 5934 (1966); Wilzbach and Kaplan, *J. Am. Chem. Soc.* **87,** 4004 (1965); and Criegee and Askani, *Angew. Chem. Intern. Ed.* **5,** 519 (1966).

[104] Masamune, Cuts, and Hogben, *Tetrahedron Letters* **1966,** 1017.

(**64**) or partially eclipsed conformations. The strain resulting from eclipsed conformations is called *Pitzer strain.* For rings from 5- to 13-membered (except for the chair form of cyclohexane) there is no escape from at least one of these two types of strain. In practice each ring adopts conformations which, as much as possible, minimize both sorts of strain. For cyclopentane, as we have seen (p. 109), this means that the molecule is not planar. In rings larger than 9-membered, Pitzer strain seems to disappear, but transannular strain is still present.[105] For 9- and 10-membered rings, some of the transannular and Pitzer strain may be relieved by the adoption of a third type of strain—*large-angle strain.* Thus, C—C—C angles of 115 to 120° have been found in x-ray diffraction of cyclononylamine hydrobromide and 1,6-diaminocyclodecane dihydrochloride.[106]



63



64

The amount of strain in cycloalkanes may be seen in Table 4, which lists heats of combustion per CH_2 group. As may be seen, cycloalkanes larger than 13-membered are as strain-free as cyclohexane.

Transannular interactions may exist across rings from 8- to 11-membered, and even larger.[107] Spectral and dipole measurements on **65** show that the carbonyl group is affected by the nitrogen.[108] **66** is probably another canon-

---

[105] Huber-Buser and Dunitz, *Helv. Chim. Acta* **43,** 760 (1960).

[106] Bryan and Dunitz, *Helv. Chim. Acta* **43,** 1 (1960); Dunitz and Venkatesan, *Helv. Chim. Acta* **44,** 2033 (1961).

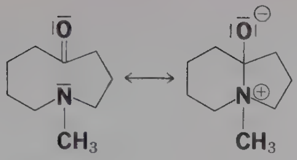
[107] For a review, see Cope, Martin, and McKervey, *Quart. Rev. (London)* **20,** 119–152 (1966).

[108] Leonard, Fox, and Ōki, *J. Am. Chem. Soc.* **76,** 5708 (1954); Leonard, Morrow, and Rogers, *J. Am. Chem. Soc.* **79,** 5476 (1957); Leonard, *Record Chem. Progr. (Kresge-Hooker Sci. Lib.)* **17,** 243 (1956).

TABLE 4. Heats of combustion in the gas phase, in kilocalories per mole, for cycloalkanes, per CH_2 group[109]

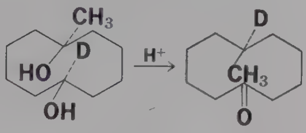
Size of ring	$-\Delta H_c(g)$	*Size of ring*	$-\Delta H_c(g)$
3	166.3	10	158.6
4	163.9	11	158.4
5	158.7	12	157.8
6	157.4	13	157.7
7	158.3	14	157.4
8	158.6	15	157.5
9	158.8	16	157.5

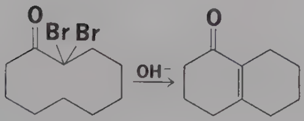
[109] Gol'dfarb and Belen'kii, Ref. 94, p. 218.

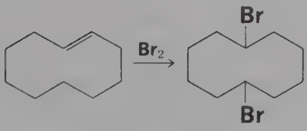


65 66

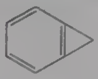
ical form. It is significant that, when this base accepts a proton, it goes to the oxygen rather than to the nitrogen. Many examples of transannular reactions are known. A few are given below.[110]







Unsaturated Rings. Cyclopropene is known but polymerizes on standing, even at −78°.[111] However, other cyclopropenes are stable.[112] The highly strained benzcyclopropene (**67**), in which the cyclopropene ring is fused to a



67

benzene ring, has been prepared[113] and is stable for weeks at room temperature, though it decomposes on distillation at atmospheric pressure.

Of course, any larger ring may contain isolated or conjugated double bonds (except for cyclobutadiene, but the extreme instability here is probably not caused entirely by strain). A stable trans double bond first appears in an 8-membered ring, and above about 11 members, the trans isomer is more stable than the cis.[52] A triple bond[114] first appears in a stable ring compound at cyclooctyne,[115] but this compound shows strain. Cyclononyne is unstrained. Transient triple bonds have been demonstrated in five-, six-, and even four-membered rings, but these have so far proved too reactive for isolation.[116] A similar statement may be made about six-membered rings with two double bonds and one triple bond (see benzynes, p. 493). The smallest cyclic allene so far prepared is 1,2-cyclononadiene,[117] but cyclic allenes are less strained than their acetylenic isomers.[118]

---

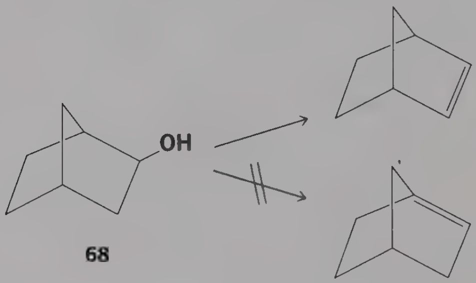
[110] References are, in the order shown, Prelog and Küng, *Helv. Chim. Acta* **39**, 1394 (1956); Schenker and Prelog, *Helv. Chim. Acta* **36**, 896 (1953); Sicher, Závada, and Svoboda, *Collection Czech. Chem. Commun.* **27**, 1927 (1962).

[111] Dem'yanov and Doyarenko, *Bull. acad. sci. Russ.* **16**, 297 (1922), *Ber.* **56**, 2200 (1923); Schlatter, *J. Am. Chem. Soc.* **63**, 1733 (1941); Wiberg and Bartley, *J. Am. Chem. Soc.* **82**, 6375 (1960).

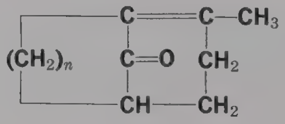
[112] For a review of cyclopropenes, see Carter and Frampton, *Chem. Rev.* **64**, 497–525 (1964).

[113] Vogel, Grimme, and Korte, *Tetrahedron Letters* **1965**, 3625. Also see Anet and Anet, *J. Am. Chem. Soc.* **86**, 526 (1964).

In bridged bicyclic compounds double bonds at the bridgehead are impossible in small systems. This is the basis of *Bredt's rule,* which states that in a case like **68,** elimination always leads away from the bridgehead. This rule no longer applies when the rings are large enough. Thus **69** ($n = 5$), a [5.3.1] system, has been prepared,[119] though the corresponding compound with $n = 4$ is not known.



68



69

Strain Due to Unavoidable Crowding. In some molecules, large groups are so close to each other that they cannot fit into the available space in such a way as to maintain normal bond angles. It has proved possible to prepare compounds with a high degree of this type of strain. For example, success has been achieved in synthesizing benzene rings containing *ortho-tert*-butyl groups. The 1,2,3-tri-*tert*-butyl compounds **70**[120] (see p. 642) and **71**[121] have been prepared, as well as the 1,2-di-*tert*-butyl compounds **72** and **73**.[122] So far no 1,2,3,4-tetra-*tert*-butylbenzene is known. That these are strained molecules is demonstrated by ultraviolet and infrared spectra, which showed that in 1,2,4-tri-*tert*-butylbenzene the ring is not planar, and by a comparison of the heats of combustion of this compound and its 1,3,5 isomer. For the 1,2,4 compound ΔH is 2657 kcal/mole, while for the 1,3,5 isomer the value is 2641 kcal/mole.[123] Even smaller groups may sterically interfere when in ortho positions. The van der Waals radius for chlorine is 1.80 Å, which means that two chlorine atoms whose centers are 3.60 Å apart or more should not interfere with each other. However, the distance between the centers of the chlorine atoms in 1,2-dichlorobenzene is 3.10 Å, so that there is crowding in this molecule.[124] There is even more crowding in *ortho*-dibromo- and diiodobenzenes. In hexaisopropylbenzene, prepared by Arnett and Bollinger, the six isopropyl groups are so crowded that they cannot rotate, but are lined up around the benzene ring, all pointed in the same direction.[125]

---

[114] For reviews of triple bonds in rings, see Wittig, *Angew. Chem. Intern. Ed. Engl.* **1,** 415–419 (1962); Kolinskii, *Russ. Chem. Rev.* **30,** 309–327 (1961).

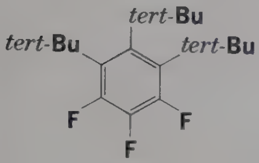
[115] Blomquist and Liu, *J. Am. Chem. Soc.* **75,** 2153 (1953).

[116] See, for example, Wittig and Mayer, *Chem. Ber.* **96,** 329, 342 (1963); Wittig and Wilson, *Chem. Ber.* **98,** 451 (1965); Wittig, Weinlich, and Wilson, *Chem. Ber.* **98,** 458 (1965); Wittig and Weinlich, *Chem. Ber.* **98,** 471 (1965).

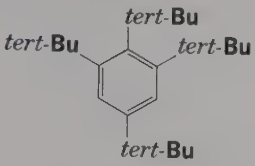
[117] Moore and Bertelson, *J. Org. Chem.* **27,** 4182 (1962). 1,2-Cyclooctadiene has been prepared, but reacts before it can be characterized (Marquis and Gardner, *Tetrahedron Letters* **1966,** 2793).

[118] Moore and Ward, *J. Am. Chem. Soc.* **85,** 86 (1963).

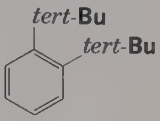
[119] Prelog, Ruzicka, Barman, and Frenkiel, *Helv. Chim. Acta* **31,** 92 (1948).



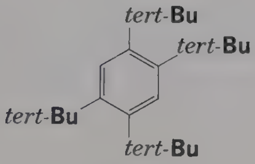
70



71



72



73

There are many other cases of intramolecular crowding resulting in distortion of bond angles. We have already mentioned hexihelicene (**11**, p. 80). The compounds tri-*tert*-butylamine and tetra-*tert*-butylmethane are as yet unknown. In the case of the latter, there is no way for the strain to be relieved, and it is questionable whether this compound can ever be made. In tri-*tert*-butylamine the crowding can be eased somewhat if the three bulky groups assume a planar instead of the normal pyramidal configuration. In the case of tri-*tert*-butylcarbinol, coplanarity of the three *tert*-butyl groups is prevented by the presence of the OH group, and yet this

[120] Viehe, Merényi, Oth, and Valange, *Angew. Chem. Intern. Ed. Engl.* **3,** 746 (1964).

[121] Arnett and Bollinger, *Tetrahedron Letters* **1964,** 3803.

[122] Hoogzand and Hübel, *Angew. Chem.* **73,** 680 (1961), *Tetrahedron Letters* **1961,** 637.

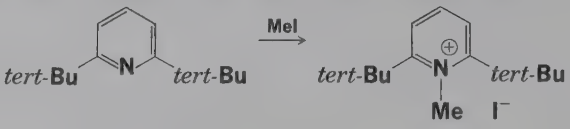
[123] Krüerke, Hoogzand, and Hübel, *Chem. Ber.* **94,** 2817 (1961); Dale, *Chem. Ber.* **94,** 2821 (1961).

[124] Struchkov and Solenova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1960,** 93.

[125] Arnett and Bollinger, *J. Am. Chem. Soc.* **86,** 4730 (1964).

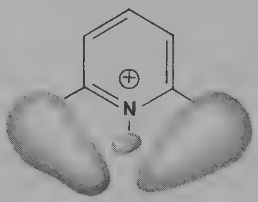
compound has been prepared.[126] Tri-*tert*-butylamine should have less steric strain than tri-*tert*-butylcarbinol, and it should be possible to prepare it.

An interesting example of steric hindrance was reported by Okamoto and Shimagawa.[127] The compound 2,6-di-*tert*-butylpyridine reacted with methyl iodide under high pressure to give the corresponding quaternary salt (**74**):



74

74 was remarkably stable, subliming under reduced pressure at 250° without decomposition. In contrast, the corresponding 2,6-dimethyl salt was completely dissociated into 2,6-dimethylpyridine and methyl iodide under these conditions. It is likely that the inert character of **74** is caused by a structure in which the methyl group is essentially imprisoned between the two bulky *tert*-butyl groups:



It is not easy to put the methyl group into its "prison" (the reaction does not succeed at ordinary pressures), and once it is there, it is not easy to get it out.

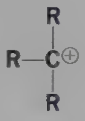
---

[126] Bartlett and Lefferts, *J. Am. Chem. Soc.* **77**, 2804 (1955).
[127] Okamoto and Shimagawa, *Tetrahedron Letters* **1966**, 317.

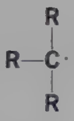
CHAPTER FIVE

Carbonium Ions, Carbanions, Free Radicals, and Carbenes

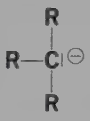
There are four known types of organic species in which a carbon atom has a valence of only two or three. These are usually very short-lived, and most are present (at least in solution) only as intermediates which are quickly converted to more stable molecules. However, some are more stable than others, and fairly stable examples have been prepared of three of the four types. The four types of species are *carbonium ions* (**1**), *free radicals* (**2**), *carbanions* (**3**), and *carbenes* (**4**).[1] Of the four, only carbanions have a complete octet around the carbon. There are many other organic ions and radicals with charges and unpaired electrons on atoms other than carbon, but these will not be discussed in this chapter.


$\mathrm{R_3C^{\oplus}}$

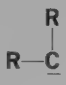
1


$\mathrm{R_3C\cdot}$

2


$\mathrm{R_3C|^{\ominus}}$

3


$\mathrm{R_2\underline{C}}$

4

We shall discuss each of the four types in a separate section, at the end of which are brief summaries of the ways in which the species form and react. These summaries are short and schematic. The generation and fate of the four types are more fully treated in appropriate places in Part 2 of this book.

CARBONIUM IONS

Stability and Structure.[2] Carbonium ions are intermediates in several kinds of reaction, and the more stable ones have been prepared in solution, and in a few cases even as solid salts. In solution the carbonium ion may be free (this is more likely in polar solvents, in which it is solvated) or may exist as an ion pair, which means that it is closely associated with a negative ion, called a *gegen-ion.* Ion pairs are more likely in nonpolar solvents.

Evidence for the existence of carbonium ions is obtained from nuclear-magnetic-resonance and other spectra, freezing-point lowering, chemical reactions, and conductivity. The latter method detects only free carbonium ions and not ion pairs.

---

[1] For a general reference on the first three types, see Leffler, "The Reactive Intermediates of Organic Chemistry," Interscience Publishers, Inc., New York, 1956.

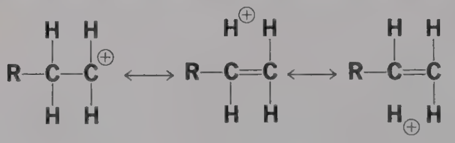
[2] For reviews see Olah and Pittman, *Advan. Phys. Org. Chem.* **4**, 305–347 (1966); Deno, *Progr. Phys. Org. Chem.* **2**, 129–193 (1964); *Chem. Eng. News* **42**, No. 40, 88 (Oct. 5, 1964); Burton, *Quart. Rev.* (*London*) **6**, 302–318 (1952); and Bethell and Gold, *Quart. Rev.* (*London*) **12**, 173–203 (1958).

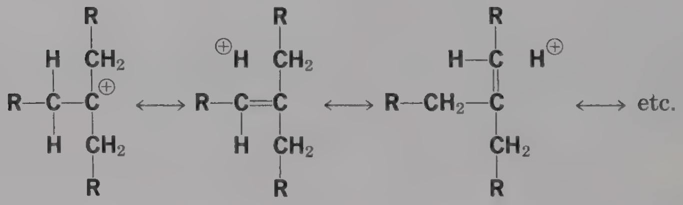
Among simple alkyl carbonium ions the order of stability is tertiary > secondary > primary. Many examples are known of rearrangements of primary or secondary systems to tertiary. Up to now, no primary aliphatic carbonium ion has lived long enough to be detected, but secondary and tertiary ions have been prepared in stable solutions by treatment of alkyl fluorides with antimony pentafluoride:[3]

$$\mathrm{RF} + \mathrm{SbF_5} \longrightarrow \mathrm{R^+} \quad \mathrm{SbF_6^-}$$

This procedure provided a dramatic example of the stability order. Both propyl fluorides gave isopropyl cation;[4] all four butyl fluorides gave *tert*-butyl cation, and all seven pentyl fluorides gave *tert*-pentyl cation. Stable simple carbonium ions have also been produced from alcohols by solution in fluorosulfonic acid–antimony pentafluoride diluted with sulfur dioxide at −60°.[5]

The stability order may be explained by hyperconjugation and by the inductive effect. If we compare a primary carbonium ion with a tertiary, it is seen that there are many more canonical forms possible for the latter:





In the examples shown the primary ion has only two hyperconjugative forms, while the tertiary has six. According to rule 6 (p. 35) the more equivalent forms, the more resonance stability. Muller and Mulliken have calculated resonance (hyperconjugation) energies for aliphatic carbonium ions:[6]

$CH_3CH_2^{\oplus}$	36 kcal/mole
$(CH_3)_2CH^{\oplus}$	66
$(CH_3)_3C^{\oplus}$	84

The inductive-effect explanation is that the electron-donating effect of alkyl groups increases the electron density at the charge-bearing carbon, reducing the net charge on the carbon and in effect spreading the charge over the α-carbons. It is a general rule that the more concentrated any charge is, the less stable will be the species bearing it.

---

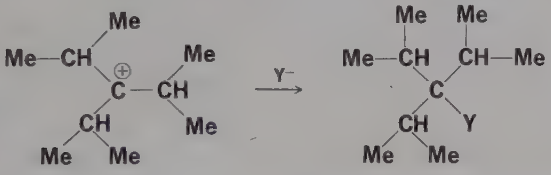
[3] Olah, Baker, Evans, Tolgyesi, McIntyre, and Bastien, *J. Am. Chem. Soc.* **86**, 1360 (1964).

[4] We adopt the nomenclature of Deno (Ref. 2). "Isopropyl carbonium ion" is ambiguous, since it could mean either Me_2CH^+ or $Me_2CHCH_2^+$.

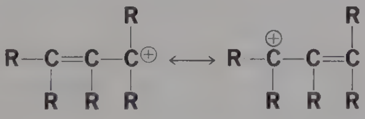
[5] Olah, Comisarow, Cupas, and Pittman, *J. Am. Chem. Soc.* **87**, 2997 (1965).

[6] Muller and Mulliken, *J. Am. Chem. Soc.* **80**, 3489 (1958).

Another factor responsible for the greater stability of tertiary carbonium ions is B-strain (see p. 234), although this becomes important only when large groups are present on the central carbon. For example, the bond angles at the central carbon of the triisopropylmethyl cation are 120°, but if a fourth group came in, the three isopropyl groups would have to crowd in together to allow the central carbon to attain the tetrahedral angle, causing the compression from nonbonded interactions known as B-strain.

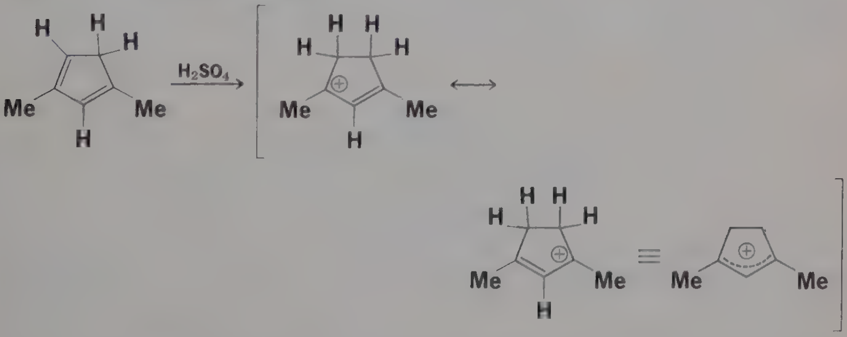


Where the positive carbon is in conjugation with a double bond, the stability should be greater, because of increased delocalization due to resonance:



$$\mathrm{R{-}\underset{R}{C}{=}\underset{R}{C}{-}\overset{R}{\underset{R}{C}}{}^{\oplus}} \longleftrightarrow \mathrm{R{-}\overset{\oplus}{\underset{R}{C}}{-}\underset{R}{C}{=}\overset{R}{\underset{R}{C}}}$$

Stable allylic-type cations have been prepared by the solution of conjugated dienes in concentrated sulfuric acid, e.g.,[7]

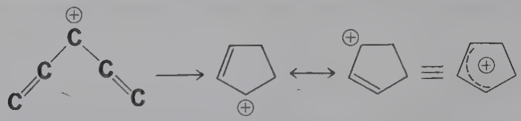


The nuclear-magnetic-resonance spectrum of this ion demonstrates that the two canonical forms indeed contribute equally. There are only three peaks, one due to the six methyl hydrogens, one to the four methylene hydrogens, and one to the single C—H hydrogen, and the area ratios are 6:4:1, as expected[7] (see p. 184). Both cyclic and acyclic allylic cations have been produced in this way. Stable allylic cations have also been obtained by the reaction between alkyl fluorides and antimony pentafluoride.[8] Divinylmethyl cations are more stable than the simple allylic type, and some of these have been prepared in concentrated sulfuric acid.[9] However, many open-chain examples cyclize to the more stable cyclic allylic type:[10]

---

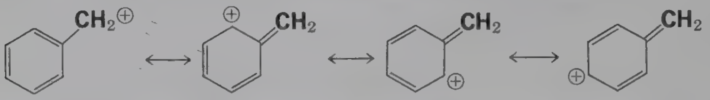
[7] Deno, Richey, Hodge, and Wisotsky, *J. Am. Chem. Soc.* **84**, 1498 (1962); Deno, Richey, Friedman, Hodge, Houser, and Pittman, *J. Am. Chem. Soc.* **85**, 2991 (1965).

[8] Olah and Comisarow, *J. Am. Chem. Soc.* **86**, 5682 (1964).



Open-chain trivinylmethyl cations are stable at low temperatures (−55°) in fluorosulfonic acid but cyclize at room temperature in this solvent or in H_2SO_4.[11] Propargyl cations have also been prepared.[12]

Similar canonical forms can be drawn for benzylic cations, e.g.,

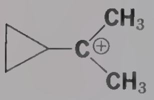


A number of benzylic cations have been isolated as the SbF_6^- salts.[13] Diphenylmethyl and triphenylmethyl cations are still more stable. Triphenylchloromethane ionizes in polar solvents which do not, like water, react with the ion. In SO_2, the equilibrium

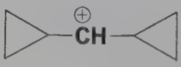
$$Ph_3CCl \rightleftharpoons Ph_3C^+ + Cl^-$$

has been known for many years. Both triphenylmethyl and diphenylmethyl cations have been isolated as solid salts.[14]

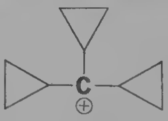
Cyclopropylmethyl cations are even more stable than the benzyl type.[15] **7** has been prepared by solution of the corresponding alcohol in 96% sulfuric acid,[16] and **5**, **6**, and similar ions by solution of the alcohols in $FSO_3H\text{-}SO_2\text{-}SbF_5$.[17] This special stability, which increases with each additional cyclopropyl group, is a result of conjugation between the bent orbitals of the cyclopropyl rings (p. 117) and the vacant *p* orbital of the carbonium ion carbon. An interesting feature of **5** is that the two methyl groups are



5



6



7

---

[9] Deno and Pittman, *J. Am. Chem. Soc.* **86,** 1871 (1964).

[10] Sorensen, *Can. J. Chem.* **42,** 2768 (1964); Deno, Pittman, and Turner, *J. Am. Chem. Soc.* **87,** 2153 (1965). Also see Ref. 9.

[11] Sorensen, *Can. J. Chem.* **43,** 2744 (1965).

[12] Pittman and Olah, *J. Am. Chem. Soc.* **87,** 5632 (1965).

[13] Cupas, Comisarow, and Olah, *J. Am. Chem. Soc.* **88,** 361 (1966); Olah, Cupas, and Comisarow, *J. Am. Chem. Soc.* **88,** 362 (1966).

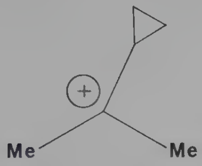
[14] Volz, *Angew. Chem. Intern. Ed. Engl.* **2,** 622 (1963); Volz and Schnell, *Angew. Chem. Intern. Ed. Engl.* **4,** 873 (1965).

[15] Deno, Richey, Liu, Lincoln, and Turner, *J. Am. Chem. Soc.* **87,** 4533 (1965).

[16] Deno, Richey, Liu, Hodge, Houser, and Wisotsky, *J. Am. Chem. Soc.* **84,** 2016 (1962).

[17] Pittman and Olah, *J. Am. Chem. Soc.* **87,** 2998 (1965); Deno, Liu, Turner, Lincoln, and Fruit, *J. Am. Chem. Soc.* **87,** 3000 (1965).

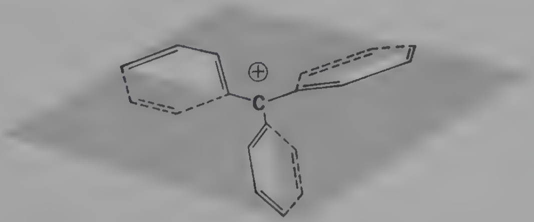
not equivalent (as shown by the nuclear-magnetic-resonance spectrum).[16] The cyclopropyl group lies closer to one side than to the other:



The stabilities of most other stable carbonium ions may also be attributed to resonance. Among these are the tropylium, cyclopropenium, and other aromatic cations discussed in Chapter 2. Where resonance stability is completely lacking, as in the phenyl cation, the ion is usually very short-lived. However, simple acyl cations, RCO^+, have been prepared, in solution and in the solid state.[18] The 2,4,6-trimethylbenzoyl and 2,3,4,5,6-pentamethylbenzoyl cations are especially stable and are easily formed in 96% H_2SO_4.[19] Acyl cations of the type R_3CCO^+ have not been obtained, because these lose CO to give the relatively stable R_3C^+ ions.

Since the central carbon of carbonium ions has only three bonds, and no other valence electrons, the bonds are sp^2 and should be planar.[20] Infrared spectra of simple alkyl carbonium ions show this to be so.[3] Other evidence is that carbonium ions are difficult or impossible to form at bridgeheads, where they cannot be planar (see p. 258). However, the adamantyl cation has been prepared, as the SF_6^- salt.[21] This represents an unusual type of bridgehead carbonium ion, and it may be planar or near-planar even though the positive charge is at a bridgehead (see p. 258).

Triarylmethyl cations are probably propeller-shaped, though the central carbon and the three ring carbons connected to it are in a plane:[22]



Of course, solvated carbonium ions, or carbonium ions in ion pairs, need not be planar.

Assuming that the solvent does not react with the carbonium ion, the more polar the solvent, the more stable are carbonium ions.

---

[18] Olah, Kuhn, Tolgyesi, and Baker, *J. Am. Chem. Soc.* **84,** 2733 (1962); Olah, Tolgyesi, Kuhn, Moffatt, Bastien, and Baker, *J. Am. Chem. Soc.* **85,** 1328 (1963); Deno, Pittman, and Wisotsky, *J. Am. Chem. Soc.* **86,** 4370 (1964).

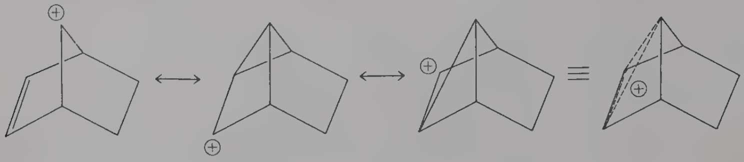
[19] Hammett and Deyrup, *J. Am. Chem. Soc.* **55,** 1900 (1933); Newman and Deno, *J. Am. Chem. Soc.* **73,** 3651 (1951).

[20] For a discussion of the stereochemistry of carbonium ions, see Eliel, "Stereochemistry of Carbon Compounds," pp. 372–380, McGraw-Hill Book Company, New York, 1962.

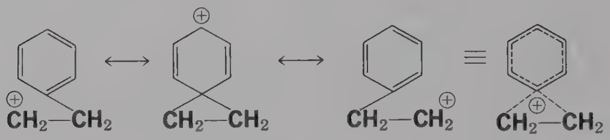
[21] Schleyer, Fort, Watts, Comisarow, and Olah, *J. Am. Chem. Soc.* **86,** 4195 (1964).

[22] Sharp and Sheppard, *J. Chem. Soc.* **1957,** 674.

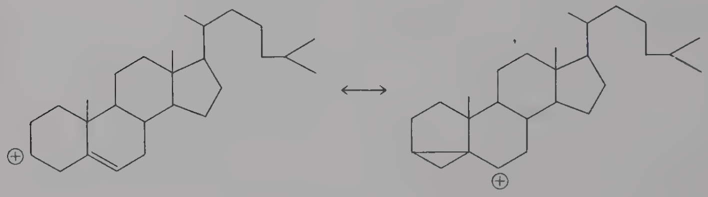
Nonclassical Carbonium Ions.[23] There are two types of *nonclassical* (also called *bridged*) *carbonium ions.* For one type, which may be called *electron-sufficient* nonclassical carbonium ions,[24] canonical forms may be drawn which involve unsaturation *which is not on the adjacent atom.* Examples are



8



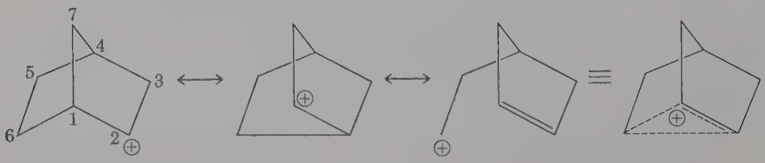
9 **14**



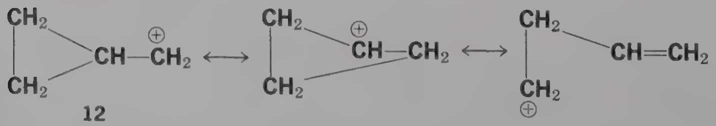
10

8, **9**, and **10** are called *homoallylic* carbonium ions, since there is one carbon atom between the positive charge and the unsaturation.

For the second type, called *electron-deficient* nonclassical carbonium ions, we may draw canonical forms which do not involve unsaturation at all. These canonical forms involve overlap with the σ orbitals of carbon-carbon single bonds. Examples are



11

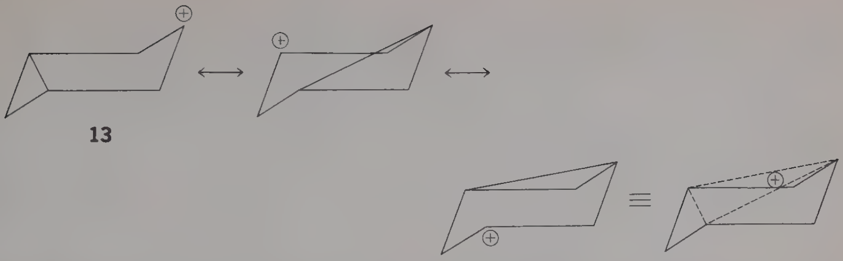


12

---

[23] For a monograph, see Bartlett, *Nonclassical Ions. Reprints and Commentary,* W. A. Benjamin, Inc., New York, 1965. For a review, see Sargent, *Quart. Rev.* (*London*) **20,** 301-371 (1966).

[24] The terms electron-sufficient and electron-deficient, used for nonclassical carbonium ions, are due to Brown, Morgan, and Chloupek, *J. Am. Chem. Soc.* **87,** 2137 (1965).

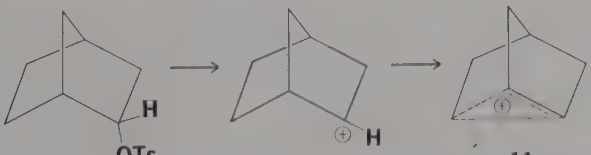


13

Carbonium ion **13** is called *homoaromatic* because, if the resonance shown is actually there, it is an aromatic ring of two electrons.

In recent years a controversy has arisen as to whether there actually are nonclassical carbonium ions. It is not doubted that ions **8** to **13** exist (as intermediates), but some workers, most notably H. C. Brown,[25] contend that there are no delocalizations of the type shown or that the importance of such delocalization has been greatly overemphasized. In the next few pages we shall examine some of the evidence which bears on this controversy, although a thorough discussion would be beyond the scope of this book.[23] The question of the existence of nonclassical carbonium ions is closely related to the question of whether aryl groups, carbon-carbon single bonds, and carbon-carbon double bonds can lend neighboring-group assistance to ionization (see p. 267). In the arguments presented by one side or the other, the distinction between neighboring-group participation and the existence of nonclassical carbonium ions has not always been kept clear.[26] If a nonclassical carbonium ion exists in any reaction, then an ion with electron delocalization, as shown in the above examples, is a discrete reaction intermediate. If a carbon-carbon double or single bond assists in the removal of a leaving group to form a carbonium ion, it may be that a nonclassical carbonium ion is involved, but there is no necessary relation. There are four possibilities:

1. The leaving group may depart without assistance and *then* a nonclassical ion may form, e.g. (as we shall see later),



11

Classical carbonium ion

Nonclassical carbonium ion

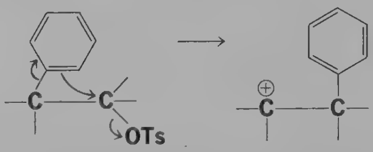
---

[25] Brown, in "The Transition State," *Chem. Soc. (London) Spec. Publ.* **16,** 140–158 (1962); *Chem. Brit.* **1966,** 199–208; Ref. 24, Hückel, *J. prakt. Chem.* [4] **28,** 27 (1965).

[26] This has been pointed out by Cram, *J. Am. Chem. Soc.* **86,** 3767 (1964).

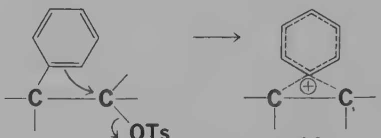
In this case there is no rate enhancement (compared, say, to the same reaction run on cyclopentyl tosylate, where no nonclassical ion is involved at any time).

2. A carbon-carbon double or single bond may lend assistance (see p. 267) but may nonetheless give a classical ion, e.g.,



In this case the rate *would* be enhanced, though no nonclassical ion is involved.

3. Both assistance and a nonclassical ion may be involved, e.g.,



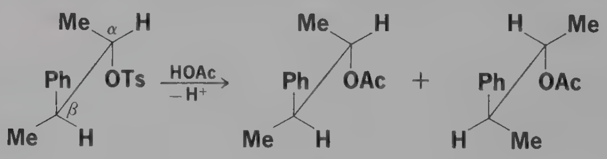
14

4. And, of course, there may be unassisted ionization to a classical carbonium ion.

Enhanced rates are usually evidence for neighboring-group assistance but are not *always* evidence for the existence of nonclassical carbonium ions.

The following is some of the evidence for and against the existence of electron-sufficient nonclassical carbonium ions (types **8** to **10**):

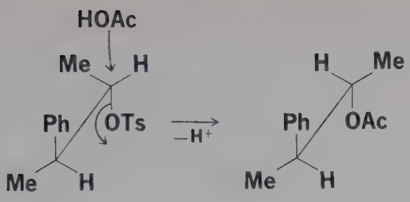
1. When the tosylate (**15**) of L-*threo*-3-phenyl-2-butanol was solvolyzed in acetic acid, 96% of the acetate product was the threo isomer.[27] Only 4% of the erythro isomer was produced. Moreover, both the D and the L threo isomers (**16** and **17**) were produced in approximately equal amounts (a racemic mixture). When solvolysis was conducted in formic acid, even less erythro isomer was obtained. If the acetic acid attacked the α-carbon as the OTs was leaving (S_N2 mechanism, see p. 251), the product would have been one of the erythro isomers, and no threo isomers would have been produced:



15 **16** **17**

---

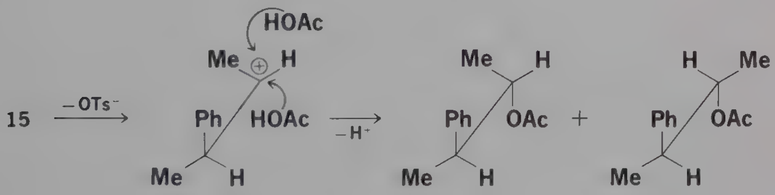
[27] Cram, *J. Am. Chem. Soc.* **71**, 3863 (1949).



15 **18**

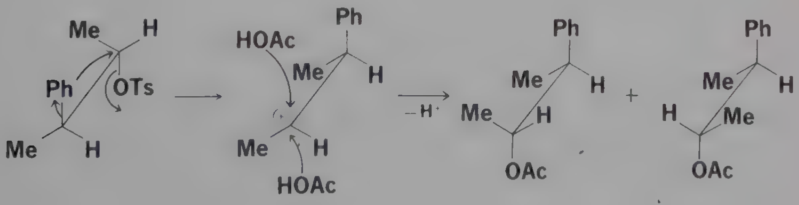
Erythro

If the tosyl group departed to give an open carbonium ion and then the acid attacked, the stereochemistry at the β position would be unaffected, but the acid could attack the planar carbonium ion at the α position from either side. Hence a mixture of **16** and **18** (not necessarily in equal amounts) would be formed, but no **17**.



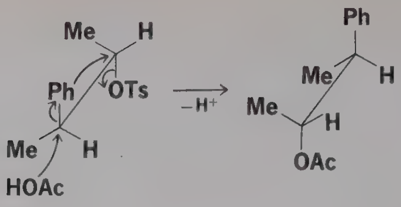
19 **16** **18**

If the phenyl provided assistance to the leaving of the tosyl group, but no nonclassical ion were formed because the bond between the phenyl and the β-carbon was simultaneously breaking (a possibility mentioned on p. 132), then the stereochemistry at the α-carbon would be inverted, and both possibilities would be formed at the β-carbon, so that the products would be **17** and the other erythro isomer, but no **16**.



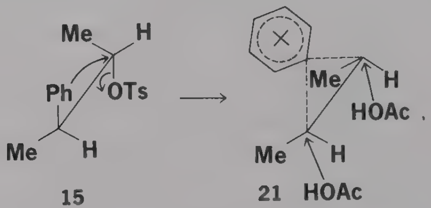
15 **20** **17**

Finally, if the acetic acid attacked while the migration was taking place, there would be no intermediate cation at all, and the product would be exclusively **17**.



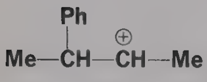
15 **17**

Obviously, none of these pathways is followed, since none explains why 95% **16** and **17** (and in virtually equal amounts) are obtained. Cram[27] explained the results by postulating the formation of a nonclassical intermediate (**21**) of the type **14:**



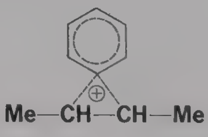
15 **21**

21 is symmetrical and so should be attacked with equal probability at either carbon, but *always from the bottom,* to give equal amounts of **16** and **17.** There could be no attack from the top, because S_N2 reactions always occur with backside attack (see p. 251). If this explanation is correct, then the nonclassical structure is more stable than either open ion, which is to be expected from the additional resonance:

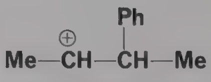


$$\mathrm{Me{-}\overset{Ph}{C}H{-}\overset{\oplus}{C}H{-}Me}$$

19



21



$$\mathrm{Me{-}\overset{\oplus}{C}H{-}\overset{Ph}{C}H{-}Me}$$

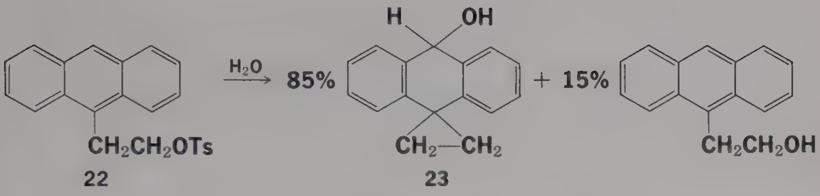
20

The alternative explanation for the stereospecificity[24,25] is that **19** *is* formed but that it rapidly equilibrates with **20,** so that **21** is a transition state and not an intermediate. Rapid equilibrium, according to this view, explains why equal amounts of the two isomers are formed, and the presence of the phenyl group on the "top" side of the molecule explains why very little acetic acid attacks from that side. Brown further points out that solvolysis reactions of systems such as **15** do not show significant rate enhancements over similar systems *not* containing a phenyl group.[28]

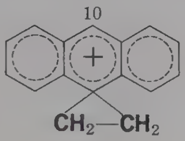
---

[28] For a reply to the arguments favoring open-chain intermediates, see Ref. 26.

2. Hydrolysis of **22** gave 85% **23**:[29]

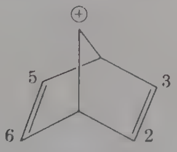


It is difficult to visualize how **23** could be easily formed from a pair of rapidly equilibrating open ions, but attack of water at the 10-position of **24** leads directly to this product. Furthermore, **24** is stable as the SbF_5OH^- salt,[30] and the nuclear-magnetic-resonance spectrum of this salt shows that the four CH_2 protons are equivalent. This would be expected either for **24** or a pair of rapidly equilibrating open ions, but the CH_2 peak is located far from the position expected for CH_2^+ protons, judging from the known positions of the protons in the isopropyl cation.[31] However, it must be pointed out that the fact that **24** is a nonclassical ion in strongly acidic solution does not necessarily mean that it is an intermediate under ordinary solvolysis conditions, though it does indicate, at least, that it is capable of existence.



24

3. The ion **25** is stable enough to be examined by nuclear magnetic resonance. The spectrum shows that the 2 and 3 protons are not equivalent to the 5 and 6 protons.[32] There is thus an interaction between the charged carbon and one double bond, which is evidence for resonance in **8**. The stability of **8** (it is stable in 96% H_2SO_4)[33] is further evidence, since without resonance interaction, this would be an ordinary secondary alkyl cation.



25

---

[29] Eberson, Petrovich, Baird, Dyckes, and Winstein, *J. Am. Chem. Soc.* **87**, 3504 (1965).

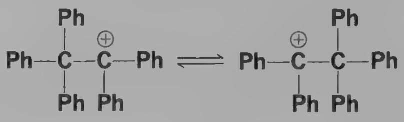
[30] Eberson and Winstein, *J. Am. Chem. Soc.* **87**, 3506 (1965).

[31] The isolation of **21** has also been reported, but this has been shown to be erroneous: Brookhart, Anet, and Winstein, *J. Am. Chem. Soc.* **88**, 5657 (1966); Olah, Pittman, Namanworth, and Comisarow, *J. Am. Chem. Soc.* **88**, 5571 (1966).

[32] Story and Saunders, *J. Am. Chem. Soc.* **84**, 4876 (1962); Story, Snyder, Douglass, Anderson, and Kornegay, *J. Am. Chem. Soc.* **85**, 3630 (1963).

[33] Winstein and Ordronneau, *J. Am. Chem. Soc.* **82**, 2084 (1960).

The above evidence strongly indicates that electron-sufficient nonclassical carbonium ions *do* exist, at least in some systems. No claim is made, for example, that *all* ions of the type represented by **9** display electron delocalization. The nuclear-magnetic-resonance spectrum of pentaphenylethyl cation (**26**), for instance, shows no evidence of a bridged structure, though the hydrogens on all the phenyl groups are equivalent, showing a rapid equilibrium.[34]

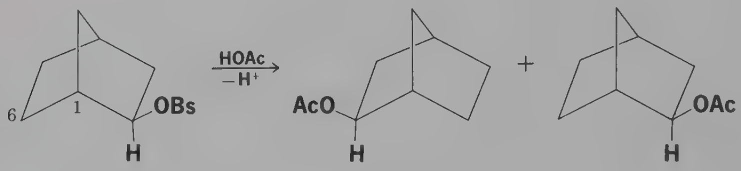


$$\mathrm{Ph{-}\overset{Ph}{\underset{Ph}{C}}{-}\overset{\oplus}{\underset{Ph}{C}}{-}Ph \rightleftharpoons Ph{-}\overset{\oplus}{\underset{Ph}{C}}{-}\overset{Ph}{\underset{Ph}{C}}{-}Ph}$$

26

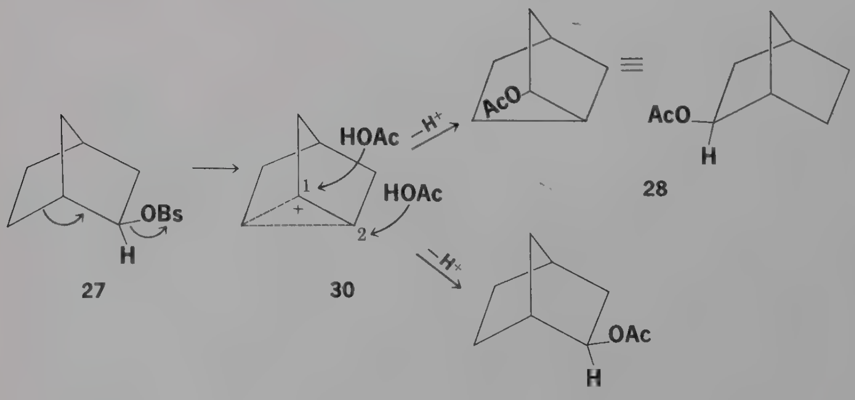
Some of the evidence bearing on the question of the existence of electron-deficient nonclassical carbonium ions is as follows:

1. Solvolysis in acetic acid of optically active *exo*-2-norbornyl brosylate (**27**) gives a racemic mixture of the two exo acetates;[35] no endo isomers are formed.[36]



27 **28** **29**

There are only two pathways which can explain this result. Either the 1,6-bond assists in the removal of the leaving group to give a nonclassical carbonium ion, which can then be attacked with equal facility at the 1- or the 2-position:



27 **30** **28** **29**

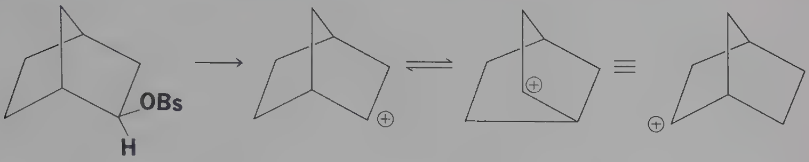
---

[34] Olah, Pittman, Namanworth, and Comisarow, *J. Am. Chem. Soc.* **88**, 5571 (1966).

[35] Winstein and Trifan, *J. Am. Chem. Soc.* **74**, 1147, 1154 (1952).

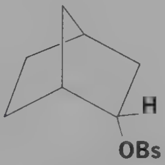
[36] It has been shown that the endo content is definitely less than 0.02%: Winstein, Clippinger, Howe, and Vogelfanger, *J. Am. Chem. Soc.* **87**, 376 (1965).

or **27** solvolyzes without participation of the 1,6-bond to give an open ion (**31**) which is in equilibrium with ion **32**:



27 **31** **32**

Once again, in the latter view,[25] **30** is not an intermediate, but a transition state in the rapid interconversion of **31** and **32**. This rapid interconversion has been likened to the action of a windshield wiper. Both of these explanations are compatible with exclusive exo attack,[37] since the endo and exo directions are not equivalent and the exo side is less hindered in either case. Much work has been done in attempting to distinguish between the two possibilities.[38] Here we treat only a small portion of this work. The most important evidence in favor of a nonclassical intermediate in this case is the fact that the *endo*-brosylate (**33**) solvolyzes 350 times more slowly than the exo isomer.[35] Similarly high exo-endo rate ratios have been found in many



33

other [2.2.1] systems. The significance of this result is that the 1,6-bond is not in a favorable position to help push out an endo leaving group. Thus, the high exo-endo rate ratios indicate that, for the exo isomers, participation by the 1,6-bond is involved, leading to **30**. Since acetolysis of **33** also leads exclusively to the exo acetates (**28** and **29**), it is likely that the classical ion **31** is first formed in this case and then is converted to the more stable **30**. Evidence for this interpretation is that the product from solvolysis of **33** is not racemic, but contains somewhat more **29** than **28** (corresponding to 3 to 13% inversion, depending on the solvent),[36] suggesting that, when **31** is formed, some of it goes to give **29** before it can collapse to **30**.

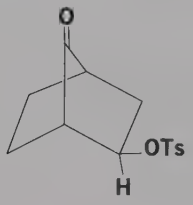
[37] In the absence of further evidence. However, it will be shown on page 138 that rapidly equilibrating ions do not give exclusive exo attack.

[38] For arguments favoring nonclassical intermediates in norbornyl systems, see, among others, Colter, Friedrich, Holness, and Winstein, *J. Am. Chem. Soc.* **87,** 378 (1965); Howe, Friedrich, and Winstein, *J. Am. Chem. Soc.* **87,** 379 (1965); Winstein, *J. Am. Chem. Soc.* **87,** 381 (1965); Berson, Hammons, McRowe, Bergman, Remanick, and Houston, *J. Am. Chem. Soc.* **87,** 3248 (1965); Schaefer and Weinberg, *Tetrahedron Letters* **1965,** 2491; and Bunton and O'Connor, *Chem. Ind. (London)* **1965,** 1182. For arguments favoring rapidly equilibrating classical ions, see, for example, Brown, Chloupek, and Rei, *J. Am. Chem. Soc.* **86,** 1246, 1247, 1248 (1964); Brown and Bell, *J. Am. Chem. Soc.* **86,** 5003, 5006 (1964); Brown and Rei, *J. Am. Chem. Soc.* **86,** 5004, 5008 (1964); and Bell and Brown, *J. Am. Chem. Soc.* **86,** 5007 (1964). Also see Refs. 23 and 25.

However, the high exo-endo rate ratios can also be interpreted in another way. It has generally been assumed that the endo rates are "normal" and the exo rates abnormally high. Brown has proposed[25] that the reverse is true: that the exo rates are "normal" and show no evidence of assistance; and that the endo rates are abnormally *low,* because of steric hindrance to removal of the leaving group in that direction.

2. It has proved possible to obtain the 2-norbornyl cation stable in solution as the SbF_6^- salt.[39] Unfortunately, hydride shifts in this ion are so rapid that no information could be obtained regarding whether it is classical or nonclassical.

3. Solvolysis of endo **34** was about six times *faster* than that of the exo isomer.[40] If there is steric hindrance to the departure of an endo group in **33,** then why not in this case? On the other hand, the presence of the electron-withdrawing C=O group α to the 1-position destabilizes any positive charge in this position, which would decrease the tendency for formation of a nonclassical ion. Since both exo and endo **34** probably ionize to classical carbonium ions, this example shows that, if anything, departure of the endo leaving group is a little *less* sterically hindered. Furthermore, acetolysis of exo **34** gave both endo and exo acetates (approximate ratio 2:3),[40] in sharp contrast to solvolysis of **27,** where only the exo product was found. This result shows that a classical carbonium ion (if indeed a classical carbonium ion is present in acetolysis of exo **34**) can be attacked from both the exo and endo positions, lending credence to the theory that the ion from exo **27,** which is attacked only from the exo side, is nonclassical. The endo isomer of **34** also gave both endo and exo acetates, but the ratio was about 2:98, showing that, if both exo and endo **34** lead to classical carbonium ions, these are not identical. Probably they both exist as ion pairs.



34

4. Ionization is accompanied by a net decrease in volume (ΔV), which should be smaller if the charge is spread out. If the endo rates are normal and the exo rates abnormally high, then ΔV for the endo compounds should be the same as that for a similar system in which only a classical ion is possible (e.g., cyclopentyl), and ΔV for the exo compound should be smaller. On the other hand, if the exo rates are normal, then ΔV for the exo case

---

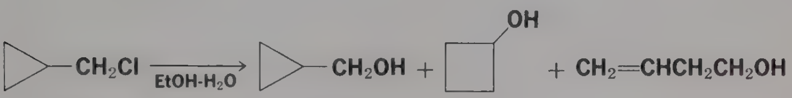
[39] Schleyer, Watts, Fort, Comisarow, and Olah, *J. Am. Chem. Soc.* **86,** 5679 (1965); Saunders, Schleyer, and Olah, *J. Am. Chem. Soc.* **86,** 5680 (1965). See also Jensen and Beck, *Tetrahedron Letters* **1966,** 4287.

[40] Gassman and Marshall, *J. Am. Chem. Soc.* **88,** 2822 (1966). See also the results of Traylor and Perrin, *J. Am. Chem. Soc.* **88,** 4934 (1966).

should be the same as that for cyclopentyl, but the endo compounds should have a greater ΔV than cyclopentyl, because of the steric hindrance. Activation volumes are determined by measuring changes in rates when reactions are run under pressure. In this case ΔV for the endo isomer of 2-norbornyl brosylate was about the same as for cyclopentyl; but the exo ΔV was significantly smaller.[41]

5. It has proved possible to calculate from bond-angle, torsional, and nonbonded strain contributions what the acetolysis rates should be for many compounds, assuming only classical ions.[42] These calculated values are less than the observed rates for acetolysis of *exo*-2-norbornyl tosylate, but not for the endo isomers. Similarly, many other compounds for which nonclassical intermediates have been proposed give calculated values below the real ones.

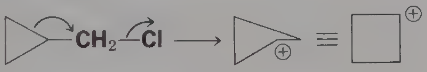
6. The products of hydrolysis of **35** are as follows:[43]



35 **36**

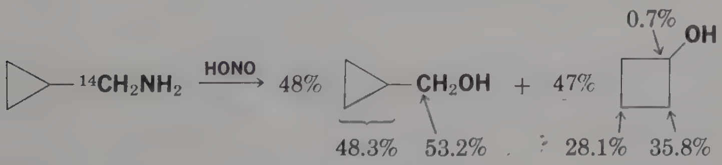
~48% ~47% ~5%

and the rate of hydrolysis is abnormally fast. If the rapid rate is due to a simple rearrangement



then it is difficult to see why half the product should be **36**. Furthermore, solvolysis of cyclobutyl chloride is also abnormally fast and gives the same mixture of products, as do both the diazotization of (cyclopropylmethyl)-amine and the solvolysis of the tosylate of buta-3-en-1-ol.[44] These results can be explained either by a nonclassical ion (**12**) or by a rapid equilibrium among open ions.

7. When diazotization was carried out on (cyclopropylmethyl)amine labeled with ^{14}C in the 1-position, the label was found distributed as follows:[45]



---

[41] le Noble and Yates, *J. Am. Chem. Soc.* **87,** 3515 (1965).

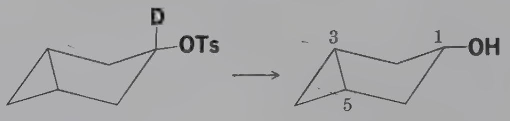
[42] Schleyer, *J. Am. Chem. Soc.* **86,** 1855, 1856 (1964). Also see Schleyer, Watts, and Cupas, *J. Am. Chem. Soc.* **86,** 2722 (1964).

[43] Roberts and Mazur, *J. Am. Chem. Soc.* **73,** 2509 (1951).

[44] Servis and Roberts, *J. Am. Chem. Soc.* **86,** 3773 (1964). Also see Closson and Kwiatkowski, *Tetrahedron* **21,** 2779 (1965).

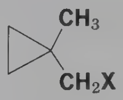
[45] Mazur, White, Semenow, Lee, Silver, and Roberts, *J. Am. Chem. Soc.* **81,** 4390 (1959). Also see Kim and Gwinn, *Tetrahedron Letters* **1964,** 2535.

Similarly, hydrolysis of **37** gave an alcohol (**38**) in which the deuterium was found equally distributed over the 1-, 3-, and 5-positions.[46] These scrambling results too are compatible with nonclassical ions (**12** and **13**) and with rapidly equilibrating classical ions.

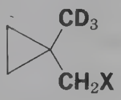


37 **38**

8. Solvolysis rates of **39** and **40** ($X = OSO_2Me$) were identical: i.e., there was no isotope effect.[47] But if the ring carbon acquires a positive charge in the transition state, there should be a secondary isotope effect (see p. 215). This is evidence *against* a nonclassical species in this case.[47a]



39



40

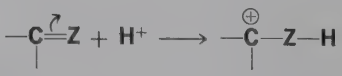
The evidence in favor of the existence of electron-deficient nonclassical carbonium ions is now quite compelling. However, it must be emphasized that, as in the case of electron-sufficient nonclassical carbonium ions, not all ions of the types represented by **11** to **13** are actually nonclassical. Some are simple open ions, and others take part in a rapid equilibrium between two or more open ions.[24] Both types of nonclassical carbonium ions are comparatively rare and are found only where steric conditions are particularly favorable for their existence.

The Generation and Fate of Carbonium Ions. Carbonium ions, stable or unstable, are most often generated in one of two general ways:

1. A direct ionization, in which a group attached to a carbon atom leaves with its pair of electrons (see Chapters 10, 13, 17, 18):

$$R\overset{\curvearrowright}{-}X \longrightarrow R^+ + X^- \qquad \text{(may be reversible)}$$

2. A proton or other positive species adds to one atom of an unsaturated system, leaving the adjacent carbon atom with a positive charge (see Chapters 11, 15, 16):



$$-\underset{|}{C}\overset{\curvearrowright}{=}Z + H^+ \longrightarrow -\underset{|}{\overset{\oplus}{C}}-Z-H$$

---

[46] Winstein and Sonnenberg, *J. Am. Chem. Soc.* **83**, 3235, 3244 (1961).

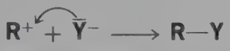
[47] Nikoletić, Borčić, and Sunko, *Pure Appl. Chem.* **8**, 441 (1964). See also Wu and Robertson, *J. Am. Chem. Soc.* **88**, 2666 (1966).

[47a] However, this result has also been explained as being consistent with a nonclassical ion: Nikoletić, Borčić, and Sunko, *Tetrahedron* **23**, 649 (1967).

Formed by either process, carbonium ions are most often short-lived transient species and react further without being isolated. There are several ways in which a carbonium ion may react, some of them giving stable products and others leading to different carbonium ions, which themselves must react further to give stable products.

The two chief pathways for carbonium-ion stabilization are the reverse of the two pathways just described.

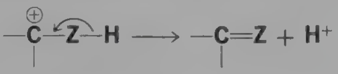
1. The carbonium ion may combine with a species possessing an electron pair (a Lewis acid-base reaction, see Chapter 8):



$$R^+ + \ddot{Y}^- \longrightarrow R{-}Y$$

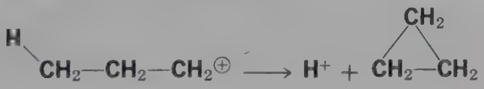
This species may be H^-, OH^-, halide ion, or any other negative ion; or it may be a neutral species with a pair to donate, in which case, of course, the immediate product must bear a positive charge (see Chapters 10, 13, 15, 16).

2. The carbonium ion may lose a proton (or much less often, another positive ion) from the adjacent atom (see Chapters 11, 17).



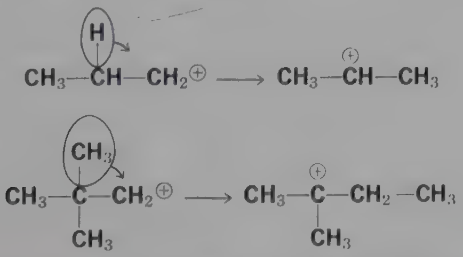
$$-\overset{\oplus}{\underset{|}{C}}-Z-H \longrightarrow -\underset{|}{C}{=}Z + H^+$$

The elimination is sometimes from a nonadjacent atom, in which case, instead of a double bond, a ring is formed.[48]

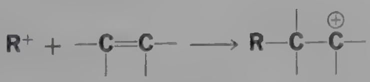


Two pathways which lead to other carbonium ions are:

3. *Rearrangement.* An alkyl or aryl group or a hydrogen (sometimes another group) migrates with its electron pair to the positive center, leaving another positive charge behind (see Chapter 18):



4. *Addition.* A carbonium ion may add to a double bond, generating a positive charge at a new position:



$$R^+ + -\underset{|}{C}{=}\underset{|}{C}- \longrightarrow R-\overset{|}{\underset{|}{C}}-\overset{\oplus}{\underset{|}{C}}-$$

41

---

[48] See, for example, Skell and Starer, *J. Am. Chem. Soc.* **82**, 2971 (1960); Silver, *J. Am. Chem. Soc.* **82**, 2971 (1960); Edwards and Lesage, *Chem. Ind.* (*London*) **1960**, 1107.

Whether formed by pathway 3 or 4, the new carbonium ion normally reacts further in an effort to stabilize itself, usually by pathway 1 or 2. However, **41** may add to another olefin molecule, and this product may add to still another, etc. This is one of the mechanisms for vinyl polymerization.

CARBANIONS

Stability and Structure.[49] There are many compounds known with a bond between carbon and a metal. Many carbon-metal bonds, for example, carbon-mercury bonds, are undoubtedly covalent, but in bonds between carbon and the more active metals the electrons are closer to the carbon. Whether the position of the electrons in a given bond is close enough to the carbon to justify calling the bond ionic, and the carbon moiety a carbanion, depends on the metal, on the structure of the carbon moiety, and on the solvent, and in many cases is a matter of speculation. In this section we shall discuss carbanions with little reference to the metal. In the next section we shall deal with the structures of organometallic compounds.

By definition, every carbanion possesses an unshared pair of electrons and is therefore a base. When it accepts a proton, it is converted into its conjugate acid (see Chapter 8). The stability of the carbanion is directly related to the strength of the conjugate acid. The weaker the acid, the greater the base strength and the lower the stability of the carbanion. By stability here we mean stability toward a proton donor: the lower the stability, the more eager the carbanion is to accept a proton from any available source and hence to end its existence as a carbanion. Thus the determination of the order of stability of a series of carbanions is equivalent to a determination of the order of strengths of the conjugate acids, and one may obtain information about relative carbanion stability from a table of acid strengths like that given in Chapter 8 (p. 219).

Unfortunately, it is not easy to measure acid strengths of very weak acids like the conjugate acids of simple unsubstituted carbanions. There is little doubt that these carbanions are very unstable in solution, and in contrast to the situation with carbonium ions, efforts to prepare solutions in which carbanions such as ethyl or isopropyl exist in a relatively free state have not yet been successful. Nevertheless, there have been several approaches to the problem. Applequist and O'Brien[50] studied the position of equilibrium for the reaction

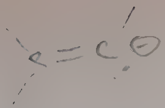
$$\mathrm{RLi + R'I \rightleftharpoons RI + R'Li}$$

in ether and in ether-pentane. The reasoning in these experiments was that the R group which forms the more stable carbanion would be more likely to

---

[49] For a monograph, see Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, 1965. For reviews, see Cram, *Pure Appl. Chem.* **7**, 155–172 (1963); *Chem. Eng. News* **41**, No. 33, 92–102 (1963), pp. 96–101; Eliel, "Stereochemistry of Carbon Compounds," pp. 384–393, McGraw-Hill Book Company, New York, 1962; and Streitwieser and Hammons, *Progr. Phys. Org. Chem.* **3**, 41–80 (1965).

[50] Applequist and O'Brien, *J. Am. Chem. Soc.* **85**, 743 (1963).



be bonded to lithium than to iodide. Carbanion stability was found to be in this order: vinyl > phenyl > cyclopropyl > ethyl > *n*-propyl > isobutyl > neopentyl > cyclobutyl > cyclopentyl. In a somewhat similar approach, Dessy and coworkers[51] treated a number of alkylmagnesium compounds with a number of alkylmercury compounds, in tetrahydrofuran, setting up the equilibrium

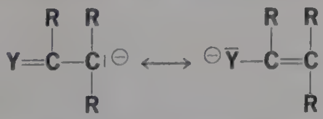
$$R_2Mg + R'_2Hg \rightleftharpoons R_2Hg + R'_2Mg$$

where the group of greater carbanion stability is linked to magnesium. The carbanion stability determined in this way was in the order phenyl > vinyl > cyclopropyl > methyl > ethyl > isopropyl. The two stability orders are in fairly good agreement, and they show that stability of simple carbanions decreases in the order methyl > primary > secondary. It was not possible by the experiments of Dessy and coworkers to determine the position of *tert*-butyl, but there seems little doubt that it is still less stable. We may interpret this stability order solely as a consequence of the inductive effect, since resonance is absent. The electron-donating alkyl groups of isopropyl result in a greater negative charge density at the central carbon atom (compared to methyl), thus decreasing its stability. The results of Applequist and O'Brien show that β branching also decreases carbanion stability. Cyclopropyl occupies an apparently anomalous position, but this is probably due to the large amount of *s* character in the carbanionic carbon (see p. 145).

A different approach to the problem of hydrocarbon acidity and hence carbanion stability was that of Shatenshtein and coworkers. These workers treated hydrocarbons with deuterated potassium amide and measured the rates of hydrogen exchange.[52] The experiments did not measure *thermodynamic* acidity, since rates were measured and not positions of equilibria. They measured *kinetic* acidity, that is, which compounds gave up protons most rapidly (see p. 204 for the distinction between thermodynamic and kinetic control of product). Measurements of rates of hydrogen exchange enable one to compare acidities of a series of acids against a given base even where the positions of the equilibria cannot be measured because they lie too far to the side of the starting materials, that is, where the acids are too weak to be converted to their conjugate bases in measurable amounts. The results of the rate measurements, too, indicated that the order of carbanion stability was methyl > primary > secondary > tertiary.[53]

Many carbanions are far more stable than the simple kind mentioned above. The increased stability is due to certain structural features:

1. Conjugation of the unshared pair with an unsaturated bond:

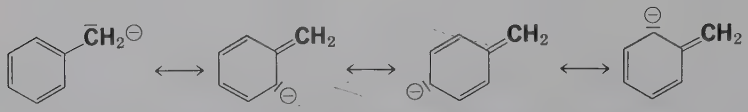


---

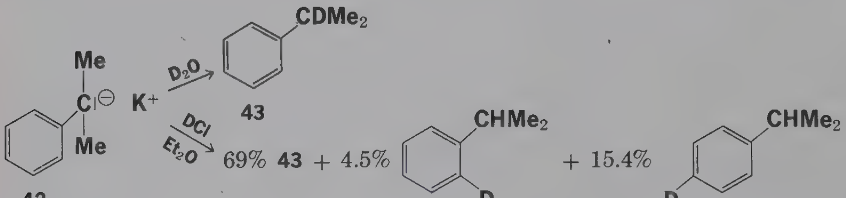
[51] Dessy, Kitching, Psarras, Salinger, Chen, and Chivers, *J. Am. Chem. Soc.* **88**, 460 (1966).
[52] For a discussion, see Shatenshtein, *Advan. Phys. Org. Chem.* **1**, 153–201 (1963).
[53] Ref. 52, pp. 175–177.

In cases where a double or triple bond is located α to the carbanionic carbon, the ion is stabilized by resonance in which the unshared pair overlaps with the π electrons of the double bond. This factor is responsible for the stability of the allylic and benzylic types of carbanions:

$$R{-}CH{=}CH{-}\bar{C}H_2^{\ominus} \longleftrightarrow R{-}\overset{\ominus}{\bar{C}H}{-}CH{=}CH_2$$

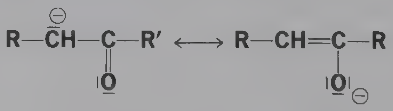


There is direct evidence for resonance in benzylic systems. When **42** was treated with D_2O, only **43** was obtained, but with DCl in ether, about 20% of the product contained deuterium in the ring.[54] Under these conditions, cumene itself did not exchange with deuterium. Diphenylmethyl and triphenylmethyl carbanions are still more stable and can be kept in solution without reacting.



42

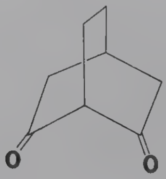
Where the carbanionic carbon is conjugated with a carbon-oxygen or carbon-nitrogen multiple bond (Y = O or N), stability of the ion is even greater, since these electronegative atoms are better capable than carbon of bearing a negative charge. However, it is questionable whether ions of this type should be called carbanions at all, since, for example, in the case of enolate ions, **45** contributes more to the hybrid than does **44**, although such ions



$$R{-}\overset{\ominus}{\bar{C}H}{-}\underset{\overset{\|}{O}}{C}{-}R' \longleftrightarrow R{-}CH{=}\underset{\overset{|}{O^{\ominus}}}{C}{-}R$$

44 **45**

more often react at the carbon than at the oxygen. Enolate ions may also be kept in stable solutions. As an interesting demonstration of the importance of resonance in the stabilization of enolate ions and of steric inhibition of resonance (see p. 36), it is observed that bicyclo[2.2.2]octa-2,6-dione



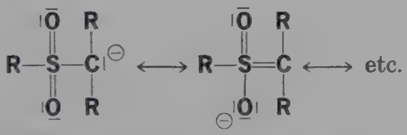
---

[54] Russell, *J. Am. Chem. Soc.* **81**, 2017 (1959).

is much less acidic than the similar compound 1,3-cyclohexadione.[55] Resonance is prohibited in the enolate ion corresponding to the former, because the unshared pair cannot overlap with the π electrons of either C=O bond.

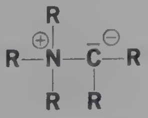
2. *Carbanions increase in stability with an increase in the amount of s character at the carbanionic carbon.* Thus the order of stability is $RC{\equiv}C^- > R_2C{=}CH^- \sim Ar^- > R_3C{-}CH_2^-$. Acetylene, where the carbon is *sp* hybridized with 50% *s* character, is much more acidic than ethylene (sp^2, 33% *s*), which in turn is more acidic than ethane, with 25% *s* character. Increased *s* character means that the electrons are closer to the nucleus and hence of lower energy. As previously mentioned, cyclopropyl carbanions are more stable than methyl, owing to the larger amount of *s* character as a result of strain (see p. 117).

3. *Conjugation of the unshared pair with a d orbital.* Where a carbanionic carbon is directly attached to an atom in the second row of the periodic table (sulfur, phosphorus, etc.), there is overlap of the unshared pair with an empty *d* orbital. For example, the SO_2R group stabilizes carbanions in this way:



Evidence that this type of conjugation is important in stabilizing such ions comes from a study of H-D exchange rates of Me_4N^+, Me_4P^+, and Me_3S^+.[56] Me_4P^+ exchanged 2.4×10^6 times faster than Me_4N^+. There is no normal conjugation in these ions, and the inductive withdrawing effect of positive nitrogen is greater than that of positive phosphorus, so that the only factor which could be causing the increased acidity is the presence of unoccupied low-lying *d* orbitals of the phosphorus. An even greater rate ratio ($2.0 \times 10^7{:}1$) was found for Me_3S^+ compared to Me_4N^+.

4. *Inductive effects.* Most of the groups which stabilize carbanions by resonance effects (either the kind discussed in paragraph 1 above or the kind discussed in paragraph 3) have electron-withdrawing inductive effects and by means of this stabilize the carbanion further by spreading the negative charge, though it is difficult to separate the inductive effect from the resonance effect. However, in a nitrogen ylide (see p. 42), where a positive nitrogen is adjacent to the carbanionic carbon, only the inductive effect is operating:



Ylides are more stable than the corresponding simple carbanions.

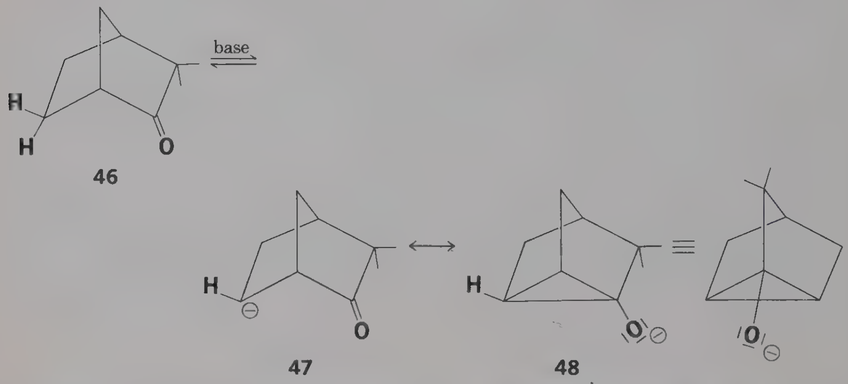
5. Certain carbanions are stable because they are aromatic (see the cyclopentadienyl anion, p. 41).

---

[55] Bartlett and Woods, *J. Am. Chem. Soc.* **62**, 2933 (1940).

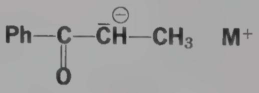
[56] Doering and Hoffmann, *J. Am. Chem. Soc.* **77**, 521 (1955).

6. *Stabilization by nonclassical resonance.* There have been far fewer reports of nonclassical carbanions than of nonclassical carbonium ions. One that may be mentioned is **48**, formed when optically active camphenilone (**46**) was treated with a strong base (potassium *tert*-butoxide).[57] That **48** was truly formed was shown by the following facts: (1) A proton was abstracted; ordinary CH_2 groups are not acidic enough for this base; (2) recovered **46** was racemized: **48** is symmetrical and can be attacked equally well from either side; (3) when the experiment was performed in deuterated solvent, the rate of deuterium uptake was equal to the rate of racemization; and (4) recovered **46** contained up to three atoms of deuterium per molecule, though if **47** were the only ion, no more than two could be taken up.



46 **47** **48**

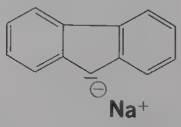
It is unlikely that free carbanions exist in solution. Like carbonium ions, they are usually in ion pairs or else solvated. Among experiments which demonstrated this was the treatment of **49** with ethyl iodide, where M was



$$Ph-\underset{\underset{O}{\|}}{C}-\overset{\ominus}{\bar{C}H}-CH_3 \quad M^+$$

49

lithium, sodium, or potassium. The half-lives of the reaction were[58] for Li, 31×10^{-6}; Na, 0.39×10^{-6}; and K, 0.0045×10^{-6}, demonstrating that the species involved were not identical. Hogen-Esch and Smid have shown that sodium fluorenide



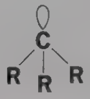
---

[57] Nickon and Lambert, *J. Am. Chem. Soc.* **88,** 1905 (1966). Also see Brown and Occolowitz, *Chem. Commun.* **1965,** 376; Nickon, Lambert, and Oliver, *J. Am. Chem. Soc.* **88,** 2787 (1966).

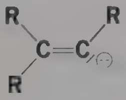
[58] Zook and Gumby, *J. Am. Chem. Soc.* **82,** 1386 (1960).

exists in tetrahydrofuran at room temperature as an intimate ion-pair, but at −80° as a solvent-separated ion-pair (that is, molecules of solvent are between the two ions).[59] This was shown by a study of the change in the visible and ultraviolet spectrum of the solution on going from 25 to −80°: a peak at 355 mμ disappears, while new peaks appear at 373 and 521 mμ. The species are therefore different, but neither is the free carbanion, since neither solution showed appreciable conductivity. Where ion-pairs are unimportant, carbanions are solvated. Cram[49] has demonstrated solvation of carbanions in many solvents.

The structure of simple unsubstituted carbanions is not known with certainty, but it seems likely that the central carbon is sp^3 hybridized, with the unshared pair occupying one apex of the tetrahedron. Carbanions would thus have pyramidal structures, similar to those of amines:



If this structure is correct, then if the three R groups are different, the carbanion should be asymmetric (see Chapter 4), and reactions in which it is an intermediate should give retention of configuration. Attempts have been made to demonstrate this, but without success.[60] A possible explanation is that the umbrella effect exists here, as in amines, so that the unshared pair and the central carbon rapidly oscillate from one side of the plane to the other. There is, though, other evidence for the sp^3 nature of the central carbon and for its tetrahedral structure. Carbons at bridgeheads, though extremely reluctant to undergo reactions in which they must be converted to carbonium ions, undergo with ease reactions in which they must be carbanions, and stable bridgehead carbanions are known. Also, reactions at vinyl carbons proceed with retention,[61] indicating that the intermediate



has sp^2 hybridization and not the sp hybridization which would be expected in the analogous carbonium ion.

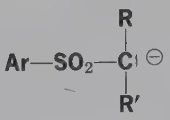
Carbanions in which the negative charge is stabilized by resonance involving overlap of the unshared-pair orbital with the π electrons of a multiple bond are essentially planar, as would be expected by the necessity for planarity in resonance, though unsymmetrical solvation or ion-pairing effects may cause the structure to deviate somewhat from true planarity.[62] Cram and coworkers have shown that where asymmetric carbanions possessing this type of resonance are generated, retention, inversion, or racemization can result depending on the solvent (see p. 447). This result is explained by unsymmetrical solvation of planar or near-planar carbanions. However, some carbanions which are stabilized by *d*-orbital overlap (p. 145), e.g.,

---

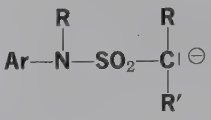
[59] Hogen-Esch and Smid, *J. Am. Chem. Soc.* **88**, 307, 318 (1966).

[60] Retention of configuration has never been observed with simple carbanions. Cram has obtained retention with carbanions stabilized by resonance. However, these carbanions are known to be planar or nearly planar, and retention was caused by asymmetric solvation of the planar carbanions (see p. 447).

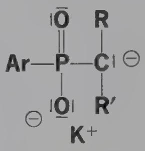
[61] Curtin and Harris, *J. Am. Chem. Soc.* **73**, 2716, 4519 (1951); Braude and Coles, *J. Chem. Soc.* **1951**, 2078; Nesmeyanov and Borisov, *Tetrahedron* **1**, 158 (1957). Also see Miller and Lee, *J. Am. Chem. Soc.* **81**, 6313 (1959); and Hunter and Cram, *J. Am. Chem. Soc.* **86**, 5478 (1964).



$\mathrm{Ar{-}SO_2{-}}\overset{R}{\underset{R'}{C}}{}^{\ominus}$

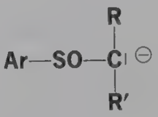


$\mathrm{Ar{-}}\overset{R}{N}\mathrm{{-}SO_2{-}}\overset{R}{\underset{R'}{C}}{}^{\ominus}$

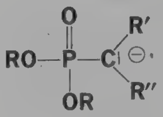


$\mathrm{Ar{-}}\overset{O}{\underset{O^{\ominus}\;K^{+}}{P}}\mathrm{{-}}\overset{R}{\underset{R'}{C}}{}^{\ominus}$

are inherently asymmetric, since retention of configuration is observed where they are generated, even in solvents which cause racemization or inversion with other carbanions.[63] Similar carbanions where the sulfur or phosphorus is bonded to one or three oxygens, e.g.,



$\mathrm{Ar{-}SO{-}}\overset{R}{\underset{R'}{C}}{}^{\ominus}$



are symmetrical.[64]

The Structure of Organometallic Compounds.[65] Whether the carbon-metal bond is ionic or polar-covalent is determined chiefly by the electronegativity of the metal and the structure of the organic part of the molecule. Ionic bonds become more likely as the negative charge on the metal-bearing carbon is decreased by inductive or resonance effects. Thus the sodium salt of acetoacetic ester has a more ionic carbon-sodium bond than does methylsodium.

Most organometallic bonds are polar-covalent. Only the alkali metals have electronegativities low enough to form ionic bonds with carbon, and even here, the behavior of lithium alkyls is more covalent than ionic. Alkyls of sodium, potassium, rubidium, and cesium are colorless nonvolatile solids insoluble in benzene or other organic solvents, while lithium alkyls are soluble,[66] though they too are almost nonvolatile. Alkyllithiums do not exist as monomeric species in benzene or ether. In benzene ethyllithium is hexameric[67] and *tert*-butyllithium is tetrameric,[68] as determined by freezing-point depression and Raman-spectra studies. Boiling-point-elevation studies have been performed in ether solutions, where alkyllithiums exist in two- to fivefold aggregates.[69] Further evidence for aggregation is that a mixture of ethyllithium and *tert*-butyllithium in benzene behaves in such a way as to indicate that it is a mixed aggregate of the two compounds.[70] Even in the gas phase, alkyllithiums exist as aggregates.[71]

---

[62] See the discussion in Cram, "Fundamentals of Carbanion Chemistry," pp. 85–105, Academic Press Inc., New York, 1965.

[63] Cram, Nielsen, and Rickborn, *J. Am. Chem. Soc.* **82,** 6415 (1960); Cram, Scott, and Nielsen, *J. Am. Chem. Soc.* **83,** 3696 (1961); Cram and Wingrove, *J. Am. Chem. Soc.* **84,** 1496 (1962); Corey and Kaiser, *J. Am. Chem. Soc.* **83,** 490 (1961); Goering, Towns, and Dittmer, *J. Org. Chem.* **27,** 736 (1962). For a discussion, see Ref. 62, pp. 105–113.

[64] Cram, Trepka, and St. Janiak, *J. Am. Chem. Soc.* **88,** 2749 (1966).

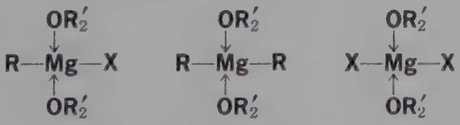
[65] For reviews, see Rochow, Hurd, and Lewis, "The Chemistry of Organometallic Compounds," pp. 15–41, John Wiley & Sons, Inc., New York, 1957; Schlosser, *Angew. Chem. Intern. Ed. Engl.* **3,** 287–306 (1964), pp. 287–291.

[66] Coates, "Organo-Metallic Compounds," pp. 3–13, Methuen & Co., Ltd., London, 1956.

It is fairly certain that the C—Mg bond in Grignard reagents is covalent and not ionic. Thus, organolithiums, organomagnesiums, and Grignard reagents have virtually identical nuclear-magnetic-resonance spectra, when the alkyl group is the same.[72] The actual structure of Grignard reagents in solution has been a matter of much controversy over the years.[73] In 1929 it was discovered[74] that the addition of dioxane to an ethereal Grignard solution precipitated all the magnesium halide and left a solution of R_2Mg in ether; that is, there could be no RMgX in the solution since there was no halide. The following equilibrium, now called the *Schlenk equilibrium*, was proposed as the composition of the Grignard solution:

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons \underset{\textbf{50}}{R_2Mg\cdot MgX_2}$$

in which **50** is a complex of some type. Since 1929 a great deal of work has been done in this area, and much evidence has been obtained for and against the Schlenk equilibrium. Some of the evidence is contradictory and mutually incompatible. This is caused partly by a failure of many investigators to use absolutely pure materials and partly by the fact that the nature of the species present in the Grignard solution seems to depend on the identity of R, X, the solvent, and the concentration.[75] However, in recent years the picture seems to be clearing up. It has been known for many years that the magnesium in a Grignard solution, no matter whether it is RMgX, R_2Mg, or MgX_2, can coordinate with two molecules of ether in addition to the two covalent bonds:



$$\underset{\overset{\uparrow}{OR'_2}}{\overset{OR'_2}{\overset{\downarrow}{R—Mg—X}}} \qquad \underset{\overset{\uparrow}{OR'_2}}{\overset{OR'_2}{\overset{\downarrow}{R—Mg—R}}} \qquad \underset{\overset{\uparrow}{OR'_2}}{\overset{OR'_2}{\overset{\downarrow}{X—Mg—X}}}$$

---

[67] Brown and Rogers, *J. Am. Chem. Soc.* **79**, 1859 (1957).

[68] Weiner, Vogel, and West, *Inorg. Chem.* **1**, 654 (1962).

[69] Wittig, Meyer, and Lange, *Ann.* **571**, 167 (1951).

[70] Weiner and West, *J. Am. Chem. Soc.* **85**, 485 (1963).

[71] Berkowitz, Bafus, and Brown, *J. Phys. Chem.* **65**, 1380 (1961); Brown, Dickerhoof, and Bafus, *J. Am. Chem. Soc.* **84**, 1371 (1962).

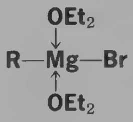
[72] Fraenkel, Adams, and Williams, *Tetrahedron Letters* **1963**, 767.

[73] For reviews, see Ashby, *Quart. Rev. (London)* **21**, 259–285 (1967); Kharasch and Reinmuth, "Grignard Reactions of Nonmetallic Substances," pp. 99–109, Prentice-Hall, Inc., Englewood Cliffs, N.J., 1954; and Salinger, *Surv. Progr. Chem.* **1**, 301–324 (1963).

[74] Schlenk and Schlenk, *Ber.* **62B**, 920 (1929).

[75] See Salinger and Mosher, *J. Am. Chem. Soc.* **86**, 1782 (1964); Kirrman, Hamelin, and Hayes, *Bull. Soc. chim. France* **1963**, 1395.

Rundle and coworkers performed x-ray-diffraction studies on solid phenylmagnesium bromide dietherate and on ethylmagnesium bromide dietherate, which they obtained by cooling ordinary ethereal Grignard solutions until the solids crystallized.[76] They found that the structures were monomeric:



$$R-\overset{\overset{OEt_2}{\downarrow}}{\underset{\underset{OEt_2}{\uparrow}}{Mg}}-Br \qquad R = \text{ethyl, phenyl}$$

These solids still contained ether. When ordinary ethereal Grignard solutions prepared from methyl bromide, methyl chloride, ethyl bromide, and ethyl chloride were evaporated at about 100° under vacuum, so that the solid remaining contained no ether, x-ray diffraction showed *no* RMgX, but a mixture of R_2Mg and MgX_2.[77] These results indicate that in the presence of ether $RMgX \cdot 2Et_2O$ is the preferred structure, while the loss of ether drives the Schlenk equilibrium to $R_2Mg + MgX_2$. However, conclusions drawn from a study of the solid materials do not necessarily apply to the structures in solution.

It has been demonstrated, by boiling-point-elevation and freezing-point-depression measurements, that, in tetrahydrofuran at all concentrations and in ether at low concentrations (up to about 0.1 *M*), Grignard reagents prepared from alkyl bromides and iodides are monomeric; that is, there are few or no molecules with two magnesium atoms.[78] Thus, part of the Schlenk equilibrium may be operating

$$2RMgX \rightleftharpoons R_2Mg + MgX_2$$

but not the other part (that is, **50** is not present in measurable amounts). That the equilibrium between RMgX and R_2Mg lies far over to the left, at least for "ethylmagnesium bromide" in ether, was shown by Smith and Becker, who mixed 0.1 *M* ethereal solutions of Et_2Mg and $MgBr_2$ and found that a reaction occurred with a heat evolution of 3.6 kcal/mole of Et_2Mg, and that the product was *monomeric* (by boiling-point-elevation measurements).[79] When either solution was added little by little to the other, there was a linear output of heat until almost a 1:1 molar ratio was reached. Addition of an excess of either reagent gave no further heat output. These results show that at least under some conditions *the Grignard reagent is largely RMgX* (coordinated with solvent), but that the equilibrium can be driven to R_2Mg by evaporation of all the ether, or by addition of dioxane.

However, Grignard reagents prepared from alkyl bromides or iodides in ether at higher concentrations (0.5 to 1 *M*), or from alkyl chlorides in ether at all concentrations, are *dimeric,*[80] so that **50** is in solution, probably in equilibrium with RMgX and R_2Mg. That is, the complete Schlenk equilibrium seems to be present. The structure of **50** may be **51** or **52**, or both may be present. In these species there is room for only one ether molecule to coordinate with each magnesium, and it is likely that they do not form in tetrahydrofuran because the greater basicity of the latter (compared to ether) prevents the extra halogen or alkyl group from coordinating with the magnesium. When the Grignard reagent from ethyl bromide was prepared in triethylamine, a much stronger base than tetrahydrofuran, only RMgX was present, as determined by evaporation of the solvent. The solids isolated contained Mg, Br, and N in a 1.0:1.0:1.0 ratio.[81] Actually, each solid contained two moles of amine, but one was lost on drying under high vacuum. In this solvent, therefore, there is no equilibrium, and RMgX is the only species.

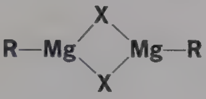
---

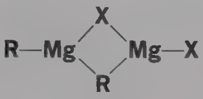
[76] Stucky and Rundle, *J. Am. Chem. Soc.* **86,** 4825 (1964); Guggenberger and Rundle, *J. Am. Chem. Soc.* **86,** 5344 (1964).

[77] Weiss, *Chem. Ber.* **98,** 2805 (1965).

[78] Ashby and Becker, *J. Am. Chem. Soc.* **85,** 118 (1963); Ashby and Smith, *J. Am. Chem. Soc.* **86,** 4363 (1964); Vreugdenhil and Blomberg, *Rec. trav. chim.* **82,** 453, 461 (1963).

[79] Smith and Becker, *Tetrahedron* **22,** 3027 (1966).


51


52

It had previously been asserted that at least in some ether solutions the Schlenk equilibrium could not be present, since a mixture of diethylmagnesium and labeled magnesium bromide gave, after 10 min or 36 hr, only about 8% exchange of magnesium.[82] If RMgX were taking part in an equilibrium, the labeling would have been scrambled. However, other experiments, in ether and in tetrahydrofuran, demonstrated statistical exchange of magnesium.[83] The reasons for the discrepancies are not known.

The Grignard reagent prepared from 1-chloro-3,3-dimethylpentane in ether undergoes rapid inversion at the magnesium-containing carbon (demonstrated by nuclear magnetic resonance—there is no optical activity in this compound).[84] The mechanism of this inversion is not known, but the reaction is probably bimolecular (that is, two molecules of organomagnesium compound are involved).

It might be mentioned that matters are much simpler for organometallic compounds with less polar bonds. Thus Et_2Hg and EtHgCl are both definite compounds, the former a liquid and the latter a solid.

The Generation and Fate of Carbanions. The two principal ways in which carbanions are generated are parallel with the ways of generating carbonium ions.

---

[80] Ashby and Smith, *J. Am. Chem. Soc.* **86**, 4363 (1964).

[81] Ashby, *J. Am. Chem. Soc.* **87**, 2509 (1965).

[82] Dessy, Handler, Wotiz, and Hollingsworth, *J. Am. Chem. Soc.* **79**, 3476 (1957). Also see Dessy and Handler, *J. Am. Chem. Soc.* **80**, 5824 (1958).

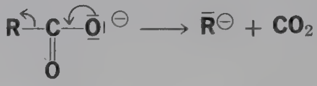
[83] Dessy, Green, and Salinger, *Tetrahedron Letters* **1964**, 1369; Cowan, Hsu, and Roberts, *J. Org. Chem.* **29**, 3688 (1964).

[84] Whitesides, Witanowski, and Roberts, *J. Am. Chem. Soc.* **87**, 2854 (1965); Whitesides and Roberts, *J. Am. Chem. Soc.* **87**, 4878 (1965).

1. A group attached to a carbon leaves without its electron pair:

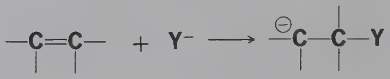
$$\text{R—H} \longrightarrow \bar{\text{R}}^{\ominus} + \text{H}^{+}$$

The leaving group is most often a proton. This is a simple acid-base reaction, and a base is required to remove the proton. However, other leaving groups are known (see Chapter 12):



$$\text{R—C(=O)—}\bar{\underline{\text{O}}}|^{\ominus} \longrightarrow \bar{\text{R}}^{\ominus} + \text{CO}_2$$

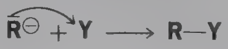
2. A negative ion adds to a carbon-carbon double or triple bond (see Chapter 15):



$$\text{—C=C—} + \text{Y}^{-} \longrightarrow {}^{\ominus}\text{C—C—Y}$$

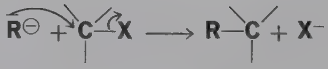
The addition of a negative ion to a carbon-oxygen double bond does not give a carbanion, since the negative charge resides on the oxygen.

The most common reaction of carbanions is combination with a positive species, usually a proton, or with another species which has an empty orbital in its outer shell (a Lewis acid-base reaction):



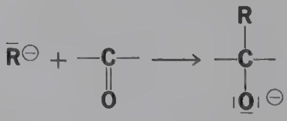
$$\bar{\text{R}}^{\ominus} + \text{Y} \longrightarrow \text{R—Y}$$

Carbanions may also form a bond with a carbon which already has four bonds, by pushing out one of the four groups (S_N2 reaction, see Chapter 10):



$$\text{R}^{\ominus} + \text{C—X} \longrightarrow \text{R—C} + \text{X}^{-}$$

Like carbonium ions, carbanions may also react in ways in which they are converted to species which are still not neutral molecules. They may add to double bonds (usually C=O double bonds; see Chapters 10 and 16),



$$\bar{\text{R}}^{\ominus} + \text{—C(=O)—} \longrightarrow \text{—C(R)(}|\underline{\text{O}}|^{\ominus}\text{)—}$$

or rearrange, though this is rare (see Chapter 18),

$$\text{Ph}_3\text{C}\bar{\text{C}}\text{H}_2^{\ominus} \longrightarrow \text{Ph}_2\overset{\ominus}{\bar{\text{C}}}\text{CH}_2\text{Ph}$$

or be oxidized to free radicals.

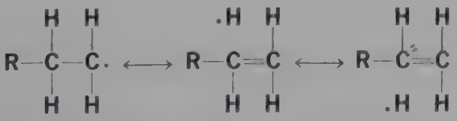
Organometallic compounds which are not ionic but polar-covalent behave very much as if they were ionic and give similar reactions.

FREE RADICALS

Stability and Structure.[85] Associated with the spin of an electron is a magnetic moment, which can be expressed by a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$. According to the Pauli principle, the two electrons in an orbital must have opposite spins, so that the total magnetic moment is zero for any two electrons occupying the same orbital. Free radicals, which have an orbital occupied by a single electron, therefore, have a net magnetic moment and are paramagnetic. They may be detected by magnetic-susceptibility and electron-paramagnetic-resonance (see p. 196) measurements. Since there is an equal probability that a given unpaired electron will have a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$, free radicals cause two lines to appear on an electronic spectrum, and are often referred to as *doublets.*

As with carbonium ions and carbanions, simple alkyl radicals are very reactive. In solution their lifetimes are extremely short, but they can be kept for relatively long periods frozen within the crystal lattices of other molecules, so that their electron-spin-resonance spectra may be measured. Even under these conditions the methyl radical decomposes with a half-life of 10 to 15 min in a methanol lattice at 77°K.[86] Simple alkyl radicals have also been detected in the gas phase, and indeed this was the first proof of their existence. In a typical experiment lead tetramethyl vapor in a stream of inert gas was passed through a glass tube which was heated at one spot. At that spot a lead mirror was deposited, and ethane was found in the condensate. When another organometallic compound, say, bismuth trimethyl, was passed through the tube, which was heated at a spot ahead of the lead deposit, then a new deposit (of bismuth) appeared at the freshly heated spot, and the old mirror disappeared, though neither the carrier gas nor the ethane product could remove the mirror. Although at this point bismuth trimethyl was being passed through the tube, lead tetraethyl was found in the condensate. The rate of disappearance of the mirror increased with increased distance between the original deposit and the new position of heating. All this and other evidence may be taken as proof of the existence of alkyl radicals,[87] which stabilized themselves by dimerization unless a metallic surface was available for reaction to give an organometallic compound.

As with carbonium ions, the stability order of free radicals is tertiary > secondary > primary, explainable by hyperconjugation, analogous to that in carbonium ions (p. 126):



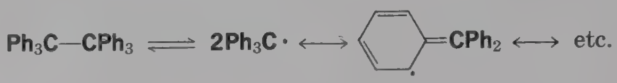
---

[85] For a monograph, see Pryor, "Free Radicals," McGraw-Hill Book Company, New York, 1966. For a review, see Wheland, "Advanced Organic Chemistry," 3d ed., pp. 731–822, John Wiley & Sons, Inc., New York, 1960.

[86] Sullivan and Koski, *J. Am. Chem. Soc.* **85,** 384 (1963).

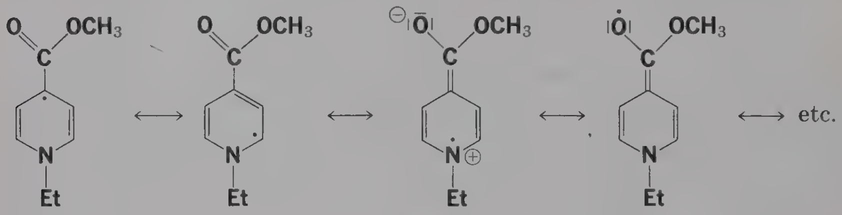
[87] Paneth and Hofeditz, *Ber.* **62,** 1335 (1929).

With resonance possibilities, the stability of free radicals increases. Thus the allyl and benzyl radicals are more stable than the simple alkyl radicals, and the triphenylmethyl and similar radicals are stable enough to exist in solution, though in equilibrium with dimeric forms:



For this case it is not certain that resonance is the only factor responsible for the stability of the radical. Steric hindrance of the phenyl groups in hexaphenylethane might also be a factor. This would be a type of B-strain.

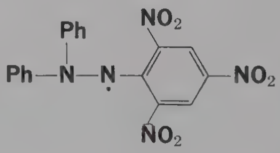
The 1-ethyl-4-carbomethoxypyridinyl radical (**53**) is more stable than the triarylmethyl type.[88] It is an emerald-green liquid which can be kept



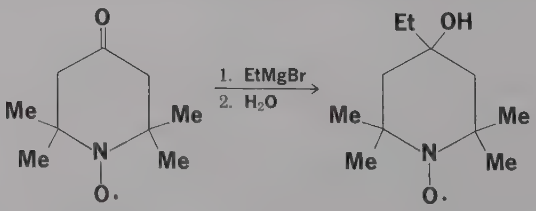
53

at room temperature in the absence of oxygen for a day or two, or in certain solvents for longer times. However, it is a highly reactive species.

Certain radicals, with the unpaired electron not on a carbon, are still more stable. Diphenylpicrylhydrazyl



is a solid which can be kept for years, and **54** is so stable that reactions can be performed on it without affecting the unpaired electron.[89]



54

---

[88] Kosower and Poziomek, *J. Am. Chem. Soc.* **86**, 5515 (1964).

[89] Neiman, Rozantsev, and Mamedova, *Nature* **200**, 256 (1963).

TABLE 1. D values (see p. 25), in kilocalories per mole, for some R—H bonds[90]
Free-radical stability is in the reverse order

R	D
$HC\equiv C\cdot$	121
$CF_3\cdot$	102–103
$CH_3\cdot$	102
$C_6H_5\cdot$	102
$C_2H_5\cdot$	98
$(CH_3)_2CH\cdot$	94
$(CH_3)_3C\cdot$	90
$CCl_3\cdot$	89–90
$HCO\cdot$	78
$C_6H_5CH_2\cdot$	77.5
$H_2C{=}CHCH_2\cdot$	77

Dissociation energies (**D** values) of R—H bonds provide a measure of the relative stability of free radicals R. Table 1 lists such values.[90] The higher the **D** value, the less stable the radical.

There are two possible structures for simple alkyl radicals.[91] They might have sp^2 bonding, in which case the structure would be planar, with the odd electron in a p orbital, or the bonding might be sp^3, which would make the structure pyramidal and place the odd electron in an sp^3 orbital. Evidence from electron paramagnetic resonance of $^{13}CH_3$ showed that the unpaired electron was in a p orbital,[92] which would show a planar structure. This is in accord with the known loss of optical activity when a free radical is generated at an asymmetric carbon. Kinetic evidence obtained from iodine exchange reactions also indicates that simple alkyl radicals are planar.[93] In addition, electronic spectra of the CH_3 and CD_3 radicals (generated by flash photolysis) in the gas phase have definitely established that under these conditions the radicals are planar or near-planar.[94]

On the other hand, the ease of obtaining bridgehead free radicals shows that a pyramidal structure is not energetically impossible, and some radical reactions have been found to proceed with some retention of optical activity,[95] although these results can also be rationalized without assuming free-radical intermediates. At any rate, it seems that the energy difference between a planar and a pyramidal free radical is not great.[91]

---

[90] These values are taken from Walling, "Free Radicals in Solution," p. 50, John Wiley & Sons, Inc., New York, 1957.

[91] For a discussion of the stereochemistry of free radicals, see Eliel, "Stereochemistry of Carbon Compounds," pp. 380–384, McGraw-Hill Book Company, New York, 1962.

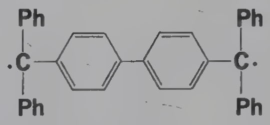
[92] Cole, Pritchard, Davidson, and McConnell, *Mol. Phys.* **1**, 406 (1958). Similar work on other ^{13}C radicals was done by Adams and Weissman, *J. Am. Chem. Soc.* **80**, 2057 (1958), and Tuttle, Ward, and Weissman, *J. Chem. Phys.* **25**, 189 (1956).

[93] Benson, Golden, and Egger, *J. Chem. Phys.* **42**, 4265 (1965), **43**, 4189 (1965). However, see Applequist, *J. Chem. Phys.* **43**, 4189 (1965), and Noyes, Applequist, Benson, Golden, and Skell, *J. Chem. Phys.* **46**, 1221 (1967).

[94] Herzberg and Shoosmith, *Can. J. Phys.* **34**, 523 (1956); Herzberg, *Proc. Roy. Soc.* (*London*) **A262**, 291 (1961).

Free radicals with resonance are planar, though triphenylmethyl-type radicals are propeller-shaped,[96] like the analogous carbonium ions (p. 129).

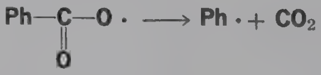
Many diradicals are known, mostly derivatives of triphenylmethyl, e.g.,



Such radicals can have total spin numbers of +1, 0, or −1, since each electron could be either $+\frac{1}{2}$ or $-\frac{1}{2}$. Spectroscopically they are called *triplets,* since each of the three possibilities is represented among the molecules and gives rise to its own spectral peak. Radicals with both unpaired electrons on the same carbon will be discussed under carbenes (p. 160).

Free Radicals—Generation and Fate.[97] Free radicals are formed from molecules by breaking of a bond so that each fragment keeps one electron. Some molecules are so unstable that this occurs spontaneously at ordinary temperatures; for example, the C—C bond energy (**D**) for hexaphenylethane is about 11 kcal/mole, and this compound, in solution, exists in equilibrium with the free radical. Usually, however, energy must be supplied by high temperatures or irradiation. Subjection of any organic molecule to a high-enough temperature in the gas phase results in the formation of free radicals. When the molecule contains bonds with **D** of 20 to 40 kcal/mole, then cleavage can be caused by heating in the liquid phase. Most often, however, free radicals are formed by photolysis of molecules—subjection to light, γ rays, etc. The energy of light of 6000 to 3000 Å is 48 to 96 kcal/mole, which is of the order of magnitude of covalent bond energies.

Free radicals are also formed from other free radicals: either by the reaction between a radical and a molecule (which *must* give another radical, since the total number of electrons is odd), or by cleavage of a radical to give another radical, e.g.,



$$\mathrm{Ph{-}\underset{\underset{O}{\|}}{C}{-}O\cdot \longrightarrow Ph\cdot + CO_2}$$

Free radicals may also be formed by oxidation or reduction, including electrolytic methods.

Reactions of free radicals either give stable products (termination reactions) or lead to other radicals, which themselves must usually react further (propagation reactions). The most common termination reactions are simple combinations of similar or different radicals:

---

[95] DeTar and Weis, *J. Am. Chem. Soc.* **79**, 3045 (1957).

[96] Adrian, *J. Chem. Phys.* **28**, 608 (1958); Andersen, *Acta Chem. Scand.* **19**, 629 (1965).

[97] For a review on formation of free radicals, see Walling, "Free Radicals in Solution," pp. 467–563, John Wiley & Sons, Inc., New York, 1957.

$$\mathrm{R\cdot} + \mathrm{R'\cdot} \longrightarrow \mathrm{R{-}R'}$$

Another termination process is disproportionation:

$$2\mathrm{CH_3{-}CH_2\cdot} \longrightarrow \mathrm{CH_3{-}CH_3} + \mathrm{CH_2{=}CH_2}$$

There are four principal propagation reactions, of which the first two are most common:

1. *Abstraction of another atom or group, usually a hydrogen atom* (see Chapter 14).

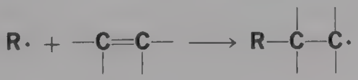
$$\mathrm{R\cdot} + \mathrm{R'{-}H} \longrightarrow \mathrm{R{-}H} + \mathrm{R'\cdot}$$

The hydrogen may also be abstracted from a position which would give the same radical, e.g.,

$$\mathrm{CH_3{-}CH_2{-}CH_2\cdot} + \mathrm{CH_3{-}CH_2{-}CH_3} \longrightarrow \mathrm{CH_3{-}CH_2{-}CH_3} + \mathrm{CH_3{-}CH_2{-}CH_2\cdot}$$

This of course leads to no net structural change.[98]

2. *Addition to a multiple bond* (Chapter 15).

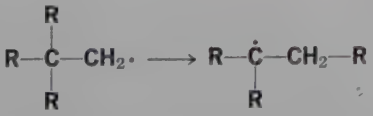


$$\mathrm{R\cdot} + -\underset{|}{\mathrm{C}}{=}\underset{|}{\mathrm{C}}- \longrightarrow \mathrm{R}-\overset{|}{\underset{|}{\mathrm{C}}}-\overset{|}{\underset{|}{\mathrm{C}}}\cdot$$

The radical formed here may add to another double bond, etc. This is one of the chief mechanisms for vinyl polymerization.

3. *Decomposition.* This may be illustrated by the decomposition of the benzoxy radical (p. 156).

4. *Rearrangement.*



$$\mathrm{R}-\overset{\mathrm{R}}{\underset{\mathrm{R}}{\mathrm{C}}}-\mathrm{CH_2\cdot} \longrightarrow \mathrm{R}-\overset{\cdot}{\underset{\mathrm{R}}{\mathrm{C}}}-\mathrm{CH_2}-\mathrm{R}$$

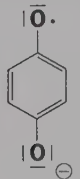
This is less common than rearrangement of carbonium ions, but it does occur (Chapter 18).

In addition to these reactions, free radicals may be oxidized to carbonium ions or reduced to carbanions.

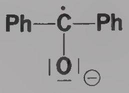
---

[98] For a review of this type of process, see Petukhov, *Russ. Chem. Rev.* **30**, 625–634 (1961).

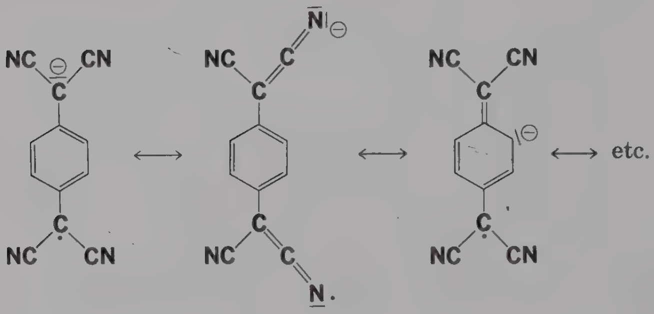
Ion-Radicals. Several types of ion-radicals are known with the unpaired electron, or the charge, or both on atoms other than carbon. Important examples are semiquinones (**55**) and ketyls (**56**). Only a few ion-radicals are known where both the unpaired electron and the charge reside on carbon atoms. One stable example is **57**.[99] Reactions in which alkali metals are reducing agents often involve ion-radical intermediates, e.g., reaction **5-12** (p. 597):[100]



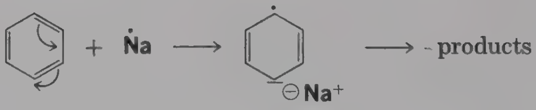
55



56



57



CARBENES

Stability and Structure.[101] *Carbenes* (also called *methylenes*) are highly reactive species, practically all having lifetimes considerably under 1 sec.[102] The only reported examples of stable carbenes are certain species where the carbene carbon is attached to two atoms each bearing an unshared pair of electrons. In such cases we may envision the following type of resonance, which would stabilize the carbene:

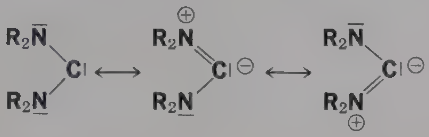
---

[99] Melby, Harder, Hertler, Mahler, Benson, and Mochel, *J. Am. Chem. Soc.* **84**, 3374 (1962).

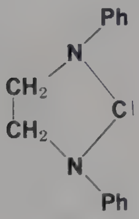
[100] For a review of anion-radicals, see McClelland, *Chem. Rev.* **64**, 301–315 (1964).

[101] For monographs, see Hine, "Divalent Carbon," The Ronald Press Company, New York, 1964; and Kirmse, "Carbene Chemistry," Academic Press Inc., New York, 1964. For reviews, see Miginiac, *Bull. Soc. chim. France* **1962**, 2000–2014; Chinoporos, *Chem. Rev.* **63**, 235–255 (1963); Kirmse, *Angew. Chem.* **73**, 161–166 (1961); *Progr. Org. Chem.* **6**, 164–213 (1964); Wanzlick, *Angew. Chem. Intern. Ed. Engl.* **1**, 75–80 (1962); Schreck, *J. Chem. Educ.* **42**, 260 (1965); Rozantsev, Fainzil'berg, and Novikov, *Russ. Chem. Rev.* **34**, 69–88 (1965); and Jerosch Herold and Gaspar, *Fortschr. chem. Forsch.* **5**, 89–146 (1966).

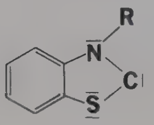
[102] Carbenes, for example, Ph_2C, F_2C, *have* been isolated by entrapment in matrixes at low temperatures (77°K or less): Murray, Trozzolo, Wasserman, and Yager, *J. Am. Chem. Soc.* **84**,



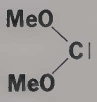
It has been reported that **58**,[103] **59**,[104] and **60**,[105] all of which can display this type of resonance, exist in equilibrium with their dimers, as the triphenylmethyl radical does (p. 154). The reactions undergone by these solutions seem to indicate that some free carbene is present. However, it was shown by crossover experiments that the dimer of **58** does not exist in equilibrium with a stable carbene.[106] Thus, a mixture of **61** and **62** did not give rise to any **63**.



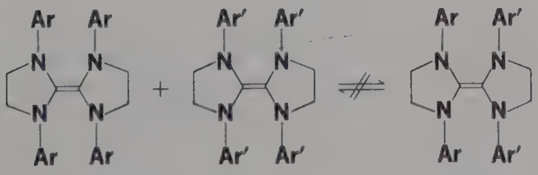
58



59



60



61 **62** **63**

Ar = phenyl
Ar′ = *p*-tolyl

3213 (1962); Trozzolo, Murray, and Wasserman, *J. Am. Chem. Soc.* **84,** 4990 (1962); Brandon, Closs, and Hutchison, *J. Chem. Phys.* **37,** 1878 (1962); Milligan, Mann, Jacox, and Mitsch, *J. Chem. Phys.* **41,** 1199 (1964); Trozzolo and Gibbons, *J. Am. Chem. Soc.* **89,** 239 (1967); and Moritani, Murahashi, Nishino, Kimura, and Tsubomura, *Tetrahedron Letters* **1966,** 373.

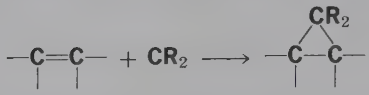
[103] Wanzlick and Schikora, *Angew. Chem.* **72,** 494 (1960), *Chem. Ber.* **94,** 2389 (1961); Wanzlick and Ahrens, *Chem. Ber.* **97,** 2447 (1964).

[104] Wanzlick and Kleiner, *Angew. Chem. Intern. Ed. Engl.* **3,** 65 (1964).

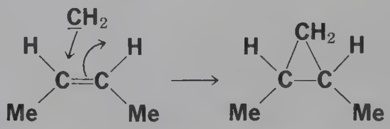
[105] Hoffmann and Häuser, *Tetrahedron Letters* **1964,** 1365.

[106] Lemal, Lovald, and Kawano, *J. Am. Chem. Soc.* **86,** 2518 (1964). See also Wanzlick, Lachmann, and Schikora, *Chem. Ber.* **98,** 3170 (1965).

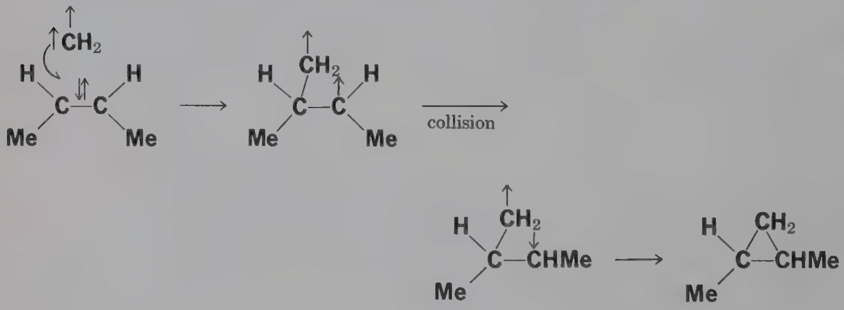
The two nonbonded electrons of a carbene may be either paired or unpaired. If they are paired, then the species is spectrally a *singlet,* while, as we have seen (p. 156), two unpaired electrons appear as a *triplet.* An ingenious method of distinguishing between the two possibilities was developed by Skell,[107] based on the common reaction of addition of carbenes to double bonds to form cyclopropane derivatives (reaction **5-37,** p. 643):



If the singlet species adds to *cis*-2-butene, then the resulting cyclopropane should be the cis isomer, since the movements of the two pairs of electrons should occur either simultaneously or with one succeeding another rapidly.



However, if the attack is by a triplet species, then the two unpaired electrons cannot *both* go into a new covalent bond, since by Hund's rule, they have parallel spins. So one of the unpaired electrons will form a bond with the electron from the double bond which has the opposite spin



leaving two unpaired electrons which cannot form a bond at once but must wait until, by some collision process, one of the electrons can reverse its spin. During this time, there is free rotation, and a mixture of *cis*- and *trans*-1,2-dimethylcyclopropanes should result.[108]

The results of this type of experiment show that CH_2 itself is usually formed as a singlet species, which can decay to the triplet state, which consequently has a lower energy. However, it is possible to prepare triplet CH_2 directly, by a photosensitized decomposition of diazomethane.[109] CH_2 is so reactive that it generally reacts as the singlet before it has a chance to decay to the triplet state. As to other carbenes, some react as triplets, some as singlets, and others as singlets or triplets, depending on how they are generated. For gaseous reactions it is possible to increase the amount of carbene which reacts as the triplet by generating the carbene in the presence of an inert gas, since collisions with these molecules cause singlet carbenes to decay to the triplet state.[110]

---

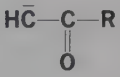
[107] Skell and Woodworth, *J. Am. Chem. Soc.* **78,** 4496 (1956).

[108] It has been maintained that this reasoning is fallacious [De More and Benson, *Advan. Photochem.* **2,** 219–261 (1964)]. For replies to this argument, see Bader and Generosa, *Can. J. Chem.* **43,** 1631 (1965), and Gaspar and Hammond, in Kirmse, "Carbene Chemistry," Ref. 101, pp. 258–272. See also Murahashi, Moritani, and Nishino, *J. Am. Chem. Soc.* **89,** 1257 (1967); and Moritani, Murahashi, Nishino, Yamamoto, Itoh, and Mataga, *J. Am. Chem. Soc.* **89,** 1259 (1967).

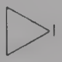
There is a limitation to the use of stereospecificity of addition as a diagnostic test for singlet or triplet carbenes. When carbenes are generated by photolytic methods, they are often in a highly excited singlet state. When they add to the double bond, the addition is stereospecific; but the cyclopropane formed carries excess energy, i.e., it is in an excited state. It has been shown that under certain conditions (low pressures in the gas phase) the excited cyclopropane may undergo cis-trans isomerization *after* it is formed, so that triplet carbene may seem to be involved although in reality the singlet was present.[111]

The most common carbenes are CH_2 and CCl_2,[112] but many others have been reported, for example,

$$\cdot\dot{C}Ph_2 \qquad R_2C{=}C{=}\bar{C}$$



$$H\bar{C}{-}\underset{\underset{O}{\|}}{C}{-}R$$



A dicarbene, $\bar{C}{=}C{=}\bar{C}$, is the major constituent of carbon vapor.[113]

Strong evidence for the geometrical structure of carbene was obtained by the study of electronic spectra of the products of flash photolysis of diazomethane.[114] Two types of CH_2 were observed, one having a linear geometry and the other a bent structure with an angle of 103°. The linear structure was found to be lower in energy and was presumed to be the ground state. This evidence is in accord with the structures we should predict for the triplet and singlet states.[115] Thus, triplet carbene should have two *sp* bonds and be linear, with the other two electrons each in an individual p orbital, while the singlet species might have two possible electronic configurations: at one extreme the central carbon might be sp^2 hybridized, with the unshared pair occupying one of the sp^2 orbitals and the remaining p orbital being vacant (so that the angle would be 120°), or, at the other extreme, there may be no hybridization, so that the bonding is p^2 (90° angle), with the unshared pair occupying the $2s$ orbital and the remaining p orbital vacant. The observed angle of 103° would seem to indicate that the singlet species displays an electronic structure which is intermediate between these two extremes.

---

[109] Kopecky, Hammond, and Leermakers, *J. Am. Chem. Soc.* **83**, 2397 (1961), **84**, 1015 (1962); Duncan and Cvetanović, *J. Am. Chem. Soc.* **84**, 3593 (1962).

[110] See Frey, *J. Am. Chem. Soc.* **82**, 5947 (1960).

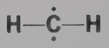
[111] Rabinovitch, Tschuikow-Roux, and Schlag, *J. Am. Chem. Soc.* **81**, 1081 (1959); Frey, *Proc. Roy. Soc. (London)* **A251**, 575 (1959).

[112] For reviews concerning CH_2, see Bell, *Progr. Phys. Org. Chem.* **2**, 1–61 (1964), and De More and Benson, Ref. 108. For a review concerning halocarbenes, see Parham and Schweizer, *Org. Reactions* **13**, 55–90 (1963).

[113] Skell and Wescott, *J. Am. Chem. Soc.* **85**, 1023 (1963).

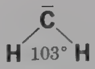
[114] Herzberg and Shoosmith, *Nature* **183**, 1801 (1959); Herzberg, *Proc. Roy. Soc. (London)* **A262**, 291 (1961).

[115] Anet, Bader, and Van der Auwera, *J. Am. Chem. Soc.* **82**, 3217 (1960).



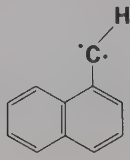
$$H-\underset{\cdot}{\dot{C}}-H$$

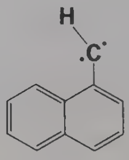
Triplet
(linear)



Singlet
(bent)

However, the triplet states of aromatic carbenes are bent. Two conformations each of 1- and 2-naphthylcarbene could be detected by electron-spin resonance:[116]





If the Ar—C—H bond were linear, only one conformation could exist.

In a case such as propargylene (**64**), resonance favors linearity even for the singlet.[117]

$$H-C\equiv C-\bar{C}-H \longleftrightarrow H-\bar{C}-C\equiv C-H$$

64

Similar species can exist with the sextet of electrons on a nitrogen atom: $R-\overline{N}|$. These have been called by various names, but the most common names are *nitrenes* and *azenes*.[118] They also are highly reactive and have many properties in common with carbenes. Silenes, R_2Si, have also been reported.[119]

Carbenes—Generation and Fate. Carbenes are chiefly formed in two ways, though other pathways are also known.

---

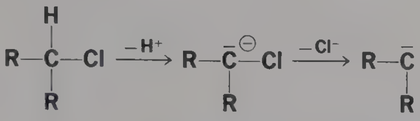
[116] Trozzolo, Wasserman, and Yager, *J. Am. Chem. Soc.* **87**, 129 (1965). Also see Wasserman, Trozzolo, Yager, and Murray, *J. Chem. Phys.* **40**, 2408 (1964).

[117] Skell and Klebe, *J. Am. Chem. Soc.* **82**, 247 (1960).

[118] For reviews, see Abramovitch and Davis, *Chem. Rev.* **64**, 149–185 (1964); Horner and Christman, *Angew. Chem. Intern. Ed. Engl.* **2**, 599–608 (1963).

[119] Skell and Goldstein, *J. Am. Chem. Soc.* **86**, 1442 (1964). For a review of carbene analogs, see Nefedov and Manakov, *Angew. Chem. Intern. Ed. Engl.* **5**, 1021–1038 (1966).

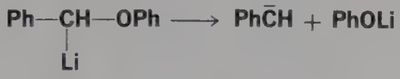
1. In α-elimination a carbon loses a group without its electron pair, usually a proton, and then a group with its pair, usually halide ion:[120]



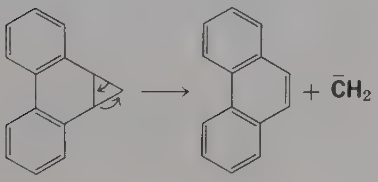
$$R_2CHCl \xrightarrow{-H^+} R_2\bar{C}^{\ominus}Cl \xrightarrow{-Cl^-} R_2\bar{C}$$

The most common example of this is formation of dichlorocarbene by treatment of chloroform with a base (see reaction **0-3**, p. 304), but many other examples are known, three of which are[121]

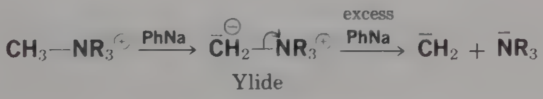
$$CCl_3{-}COO^- \xrightarrow[\Delta]{} \bar{C}Cl_2 + CO_2 + Cl^-$$



$$Ph{-}CH(Li){-}OPh \longrightarrow Ph\bar{C}H + PhOLi$$



The formation of carbenes from ylides represents a special case of this method[122]



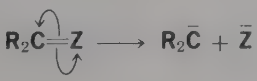
$$CH_3{-}NR_3^{\oplus} \xrightarrow{PhNa} \overset{\ominus}{\bar{C}H_2}{-}NR_3^{\oplus} \xrightarrow{\text{excess PhNa}} \bar{C}H_2 + \bar{N}R_3$$

Ylide

although doubt has been expressed as to whether a free carbene is actually formed here.[123] Indeed, many reactions in which there is an apparent α-elimination actually do not go through a carbene intermediate.

Though in most cases of α-elimination the positive group is lost first, it is also possible for the negative group to be lost first, and for the two to be lost simultaneously.

2. Disintegration of compounds containing certain types of double bonds.



$$R_2C{=}Z \longrightarrow R_2\bar{C} + \bar{Z}$$

---

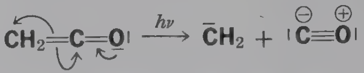
[120] For a review of formation of carbenes in this manner, see Kirmse, *Angew. Chem. Intern. Ed. Engl.* **4,** 1–10 (1965).

[121] Wagner, *Proc. Chem. Soc.* **1959,** 229; Schöllkopf and Eisert, *Ann.* **664,** 76 (1963); Richardson, Durrett, Martin, Putnam, Slaymaker, and Dvoretzky, *J. Am. Chem. Soc.* **87,** 2763 (1965).

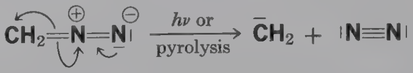
[122] Franzen and Wittig, *Angew. Chem.* **72,** 417 (1960).

[123] Hine, Ref. 101, pp. 29–30.

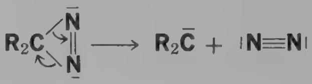
The two most important ways of forming CH_2 are examples: the photolysis of ketene



and the isoelectronic decomposition of diazomethane

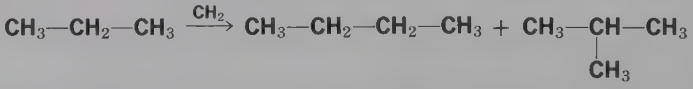


Diazirines (isomeric with diazoalkanes) also give carbenes:[124]



The reactions of carbenes are more varied than those of the other species discussed in this chapter. Additions to carbon-carbon double bonds have already been mentioned. Carbenes also add to aromatic systems, but the immediate products rearrange, usually with ring enlargement (see reaction **5-12,** p. 597). Additions of carbenes to other double bonds, such as C=N (reactions **6-62** to **6-64,** pp. 720–723), and to triple bonds, have also been reported.

An unusual reaction of carbenes is that of insertion into C—H bonds (reaction **2-11,** p. 466). Thus, CH_2 reacts with methane to give ethane, and with propane to give *n*-butane and isobutane



$$CH_3{-}CH_2{-}CH_3 \xrightarrow{CH_2} CH_3{-}CH_2{-}CH_2{-}CH_3 + CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_3$$

This reaction is virtually useless for synthetic purposes but illustrates the extreme reactivity of carbene. Treatment in the liquid phase of an alkane such as pentane with carbene formed from the photolysis of diazomethane gives the three possible products in statistical ratios,[125] demonstrating that carbene is displaying no selectivity. It is a general principle that the lower the selectivity, the higher the reactivity. CH_2 generated by photolysis of diazomethane is probably the most reactive organic species known, but CH_2 generated in other ways is somewhat less reactive, and other carbenes are still less reactive. Insertion of carbenes into other bonds has also been demonstrated, though not insertion into C—C bonds.[126]

It would seem that dimerization should be an important reaction of carbenes

$$R_2\bar{C} + R_2\bar{C} \longrightarrow R_2C{=}CR_2$$

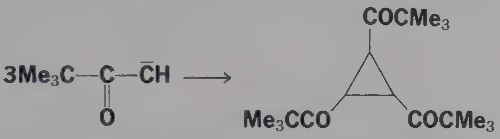
---

[124] Frey and Stevens, *Proc. Chem. Soc.* **1962,** 79; Schmitz, Habisch, and Stark, *Angew. Chem. Intern. Ed. Engl.* **2,** 548 (1963).

[125] Doering, Buttery, Laughlin, and Chaudhuri, *J. Am. Chem. Soc.* **78,** 3224 (1956); Richardson, Simmons, and Dvoretzky, *J. Am. Chem. Soc.* **83,** 1934 (1961).

[126] Doering, Knox, and Jones, *J. Org. Chem.* **24,** 136 (1959); Franzen, *Ann.* **627,** 22 (1959); Bradley and Ledwith, *J. Chem. Soc.* **1961,** 1495; Frey and Voisey, *Chem. Commun.* **1966,** 454.

but it is not, because the reactivity is so great that the carbene species do not have time to find each other, and because the dimer generally has so much energy that it dissociates again. However, apparent dimerization *has* been observed, and even trimerization:[127]

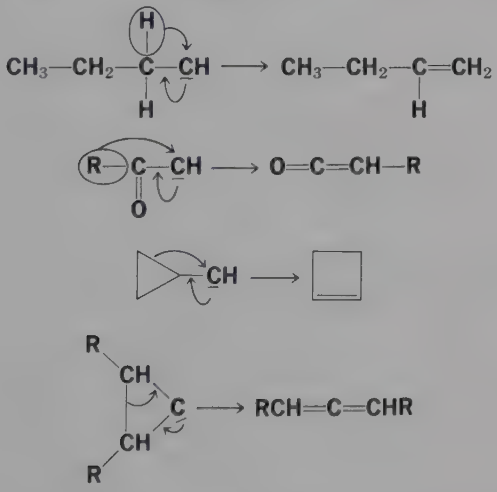


The products in many reported instances of "dimerization" probably do not arise from an actual dimerization of two carbenes but from attack by a carbene on a molecule of carbene precursor, e.g.,

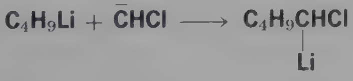
$$R_2\bar{C} + R_2CN_2 \longrightarrow R_2C{=}CR_2 + N_2$$

The same is probably true for "trimerizations."

Alkylcarbenes can undergo rearrangement, with migration of alkyl or hydrogen. Unlike rearrangement of the other species in this chapter, rearrangements of carbenes directly give stable molecules. Some examples are[128]



The rearrangement of ketocarbenes to ketenes is called the Wolff rearrangement (reaction **8-8**, p. 809). Carbenes may react with a Lewis base such as a carbanion[129] or even butyllithium:[130]



$$C_4H_9Li + \bar{C}HCl \longrightarrow C_4H_9\underset{\displaystyle Li}{\underset{|}{C}}HCl$$

---

[127] Charpentier-Morize and Colard, *Bull. Soc. chim. France* **1962**, 1982.

[128] Kirmse and Doering, *Tetrahedron* **11**, 266 (1960); Friedman and Berger, *J. Am. Chem. Soc.* **83**, 492, 500 (1961); Friedman and Shechter, *J. Am. Chem. Soc.* **82**, 1002 (1960); Moore and Ward, *J. Org. Chem.* **27**, 4179 (1962).

[129] Krapcho, Huyffer, and Starer, *J. Org. Chem.* **27**, 3096 (1962).

[130] Closs, *J. Am. Chem. Soc.* **84**, 809 (1962).

Carbenes can also abstract hydrogen to give free radicals, e.g.,

$$\bar{C}H_2 + CH_3CH_3 \longrightarrow CH_3\cdot + CH_3CH_2\cdot$$

A number of other possible carbene reactions are known but are less important.[131]

---

[131] See the monographs by Hine and Kirmse, Ref. 101.

CHAPTER SIX

Instrumental Methods for the Determination of Structure

Since 1859, when the structural theory of organic chemistry was first accepted, chemists have been determining the structures of unknown compounds, both naturally occurring and synthetic. For many years the methods used for this purpose were chiefly or even entirely chemical: reactions would be carried out on the unknown in an attempt to obtain known products, or even if unknown products were obtained, further reactions would be carried out on *them,* etc.[1]

The situation has now changed, owing to the development of a number of instrumental and other physical methods which can assist in structure determination. Although chemical methods are still widely used, instruments are playing an increasing role, and in many laboratories the burden of structure determination is mainly borne by them. There are even those who maintain that chemical methods are on the way out, or are already obsolete. A book has been written to show how the interpretation of just four types of spectra—infrared, nuclear-magnetic-resonance, electronic, and mass spectra—may be used to elucidate the structures of a large number of molecules without any other information.[2] One event which strongly emphasized to the chemical world that the old methods were giving way to the new was the structure determination of strychnine. This structure had been the object of one of the most intensive attacks in the history of organic chemistry. From the time the molecular formula, $C_{21}H_{22}O_2N_2$, was first correctly determined (in 1881) until the structure was proved in 1946,[3] more than 200 papers were published on this problem. Even then the configuration was not completely known. In contrast to this massive effort, in 1944 work was begun on the determination of the strychnine structure by x-ray crystallography. By 1951 the structure, including the configuration, had been determined by this method, and was in agreement with the result achieved chemically.[4]

In this chapter will be discussed some of the instrumental methods, with particular attention being paid to electronic and infrared spectroscopy and to nuclear magnetic resonance. Optical rotatory dispersion and circular

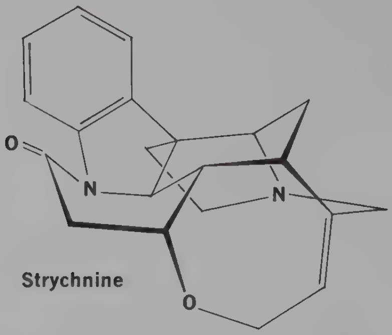
---

[1] For a review of chemical methods of structure determination, see Bentley, "Elucidation of Structures by Physical and Chemical Methods," vol. XI of Weissberger, "Technique of Organic Chemistry," part 1, pp. 457–642, part 2, pp. 643–1144, Interscience Publishers, Inc., New York, 1963.

[2] Silverstein and Bassler, "Spectrometric Identification of Organic Compounds," 2d ed., John Wiley & Sons, Inc., New York, 1967.

[3] Briggs, Openshaw, and Robinson, *J. Chem. Soc.* **1946,** 903; Holmes, Openshaw, and Robinson, *J. Chem. Soc.* **1946,** 908.

[4] Robertson and Beevers, *Acta Cryst.* **4,** 270 (1951); Bokhoven, Schoone, and Bijvoet, *Acta Cryst.* **4,** 275 (1951).



Strychnine

dichroism have already been treated (pp. 110–116). Chemical methods of structure determination are not considered in this chapter but are discussed in Part 2, each at its appropriate place in the list of reactions. It should not be expected that this chapter will make anyone proficient in the use of any technique or in the interpretation of spectra. For this, many treatises and review articles are available to which reference will be made.[5] The purpose of this chapter is to explain the basis of each method and to give some idea of how the organic chemist may use it. The uses are not limited to structure determination.

Electronic Spectra.[6] Both *visible* and *ultraviolet spectra* come under the heading of *electronic spectra,* since both are caused by electronic transitions. In Chapter 1 it was mentioned that electrons can move from the ground-state energy level to a higher one and that outside energy is required for this. This energy may be in the form of light. Light of any wavelength has associated with it an energy value given by $E = h\nu$, where ν is the frequency of the light [ν = velocity of light (c) divided by the wavelength (λ)] and h is Planck's constant. Since the energy levels of a molecule are quantized, the

---

[5] Two major compendia which treat all the important methods are Weissberger, "Physical Methods of Organic Chemistry," vol. I of Weissberger, "Technique of Organic Chemistry," 3d ed., four parts, Interscience Publishers, Inc., New York, 1960; and "Determination of Organic Structures by Physical Methods," Academic Press Inc., New York, vol. 1 edited by Braude and Nachod, 1955; vol. 2 edited by Nachod and Phillips, 1962. Two other volumes in the Weissberger series are more restricted: West, "Chemical Applications of Spectroscopy," vol. IX, 1956, deals with spectroscopic methods, and Bentley, "Elucidation of Structures by Physical and Chemical Methods," vol. XI, part 1, pp. 61–412, 1963, discusses the methods in relation to their use in structure determination. Another book which treats all the important methods, on a smaller scale, is Schwartz (ed.), "Physical Methods in Organic Chemistry," Holden-Day, San Francisco, 1964. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N.J., 1965, treats infrared, electronic, and nuclear-magnetic-resonance spectra. Also see Ref. 2.

[6] For books on electronic spectra and their interpretation, see Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold (Publishers), Ltd., London, 1958; and Jaffé and Orchin, "Theory of Ultraviolet Spectroscopy," John Wiley & Sons, Inc., New York, 1962. For a review article, see Mason, *Quart. Rev.* (*London*) **15,** 287–371 (1961). This topic is considered in the Weissberger series (see Ref. 5) by West, vol. I, part 3, pp. 1799–1958; Duncan, vol. IX, pp. 581–628; Matsen, vol. IX, pp. 629–706; and Brand and Scott, vol. XI, pp. 61–132; and in "Determination of Organic Structures by Physical Methods" (see Ref. 5) by Braude, vol. 1, pp. 131–193; Ramsay, vol. 2, pp. 246–338; and Turner (far ultraviolet), vol. 2, pp. 339–400.

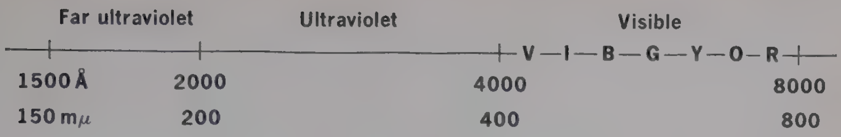


Figure 1. *The range of electronic spectra.*

amount of energy required to raise an electron in a given molecule from one level to a higher one is a fixed quantity. Only light with exactly the frequency corresponding to this amount of energy will cause the electron to move to the higher level. If light of another frequency is sent through the sample, it will pass out without a loss in intensity, since the molecules will not absorb it. However, if light of the correct frequency is passed in, the energy will be used by the molecules for electron promotion, and hence the light that leaves the sample will be diminished in intensity, or altogether gone. A *spectrophotometer* is a device which allows light of a given frequency to pass through a sample and which detects (by means of a phototube) the amount of light which has been transmitted (that is, not absorbed). The instrument compares the intensity of the transmitted light with that of the incident light. The user of a manual spectrophotometer may select visible or ultraviolet light of any frequency, pass it through the sample, and read the amount of absorption. Automatic instruments gradually and continuously change the frequency, and an automatic recorder plots a graph of absorption versus frequency or wavelength.

The energy of electronic transitions corresponds to light in the visible, ultraviolet, and far-ultraviolet regions of the spectrum (Figure 1). Absorption positions are normally expressed in wavelength units; either in angstrom units (Å) or in millimicrons (mμ). If a compound absorbs in the visible, it is colored, possessing a color complementary to that which is absorbed. Thus a compound absorbing in the violet is yellow. The far-ultraviolet region is studied by organic chemists less often than the visible or ordinary ultraviolet regions because special vacuum instruments are required, owing to the fact that oxygen and nitrogen absorb in these regions.

From these considerations it would seem that an electronic spectrum should consist of one or more sharp peaks, each corresponding to the transfer of an electron from one electronic level to another. In practice the peaks are seldom sharp. In order to understand the reason for this, it is necessary to realize that molecules are constantly vibrating and rotating and that these motions are also quantized. A molecule at any time is in a given electronic state, but also in a given vibrational and rotational state. The difference between two adjacent vibrational levels is much smaller than the difference between adjacent electronic levels, and the difference between adjacent rotational levels is smaller still. A typical situation is shown in Figure 2. When an electron moves from one electronic level to another, it moves from a given vibrational and rotational level within that electronic level to some vibrational and rotational level at the next electronic level. A given sample contains a large number of molecules, and even if all of them are in the ground electronic state, they are still distributed among the vibrational and rotational states (though the ground vibrational state V_1 is most heavily popu-

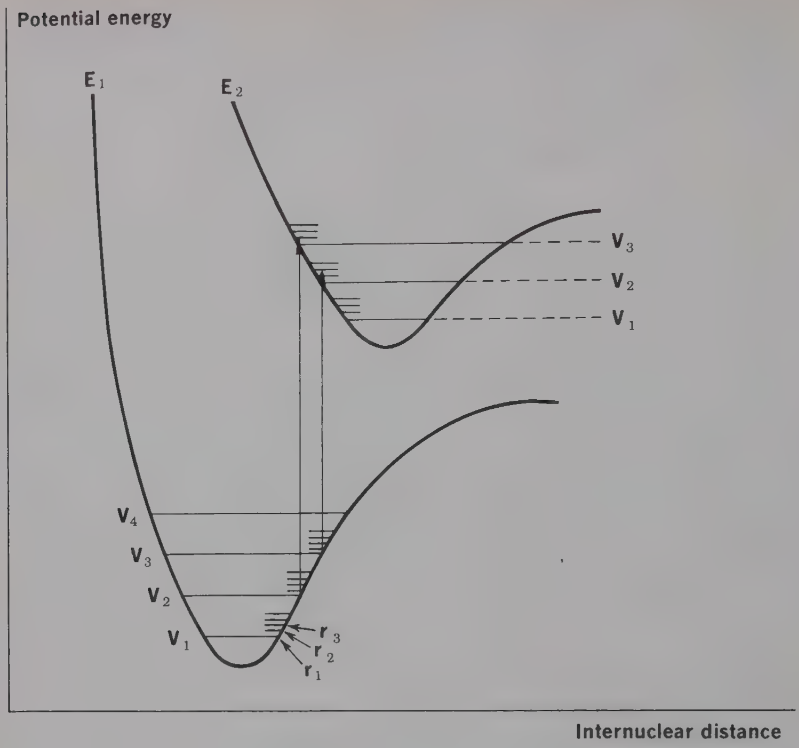


Figure 2. *Energy curves for a diatomic molecule. Two possible transitions are shown.*

lated). This means that not just one wavelength of light will be absorbed, but a number of them close together, with the most probable transition causing the most intense peak. But in molecules containing more than a few atoms there are so many possible transitions, and these are so close together, that what is observed is a relatively broad band, such as the one for methyl ethyl ketone shown in Figure 3.[7] The height of the peak is dependent on the number of molecules making the transition and is proportional to log ε, where ε is the *extinction coefficient.* The extinction coefficient may be expressed by

$$\varepsilon = \frac{E}{cl}$$

where c is the concentration in moles per liter, l is the cell length in centimeters, and $E = \log I_0/I$, where I_0 is the intensity of the incident light and I of the transmitted light. The wavelength is usually reported as λ_{max}, meaning that this is the top of the peak.

An ultraviolet or visible absorption peak is caused by the promotion of an

[7] Day, Robinson, Bellis, and Till, *J. Am. Chem. Soc.* **72,** 1379 (1950).

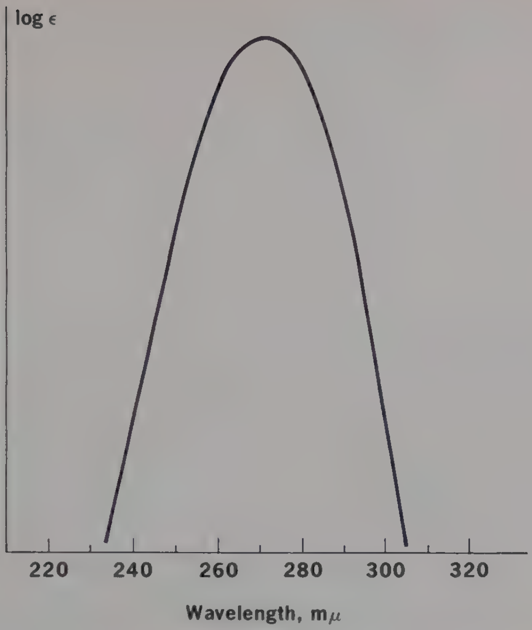


Figure 3. *Ultraviolet spectrum of methyl ethyl ketone in ethanol.*[7]

electron in one orbital (usually a ground-state orbital) to a higher orbital. Normally the amount of energy necessary to make this transition depends mostly on the nature of the two orbitals involved, and much less on the rest of the molecule. Therefore, a simple functional group such as the C=C double bond always causes absorption in the same general area. A group which causes absorption is called a *chromophore*.

Chromophores may be classified by the kinds of orbitals involved in the transition. Compounds containing only single bonds and no unshared pairs of electrons (e.g., alkanes) may only have σ-σ^* transitions, that is, promotion from a bonding σ to an antibonding σ^* orbital. The energy of such transitions is very high, and these molecules absorb below 170 mμ, which makes them transparent in the visible and ordinary ultraviolet regions. Compounds containing unshared pairs (n electrons) exhibit n-σ^* transitions, and while these have lower energies, they still fall mostly below 200 mμ and are usually of little value with ordinary instruments. For example, water absorbs at 167, methanol at 174, and chloromethane at 169 mμ.[8]

In general, only from molecules which contain unsaturation can useful information be obtained with ordinary ultraviolet instruments. Compounds containing C=C double bonds give rise to π-π^* transitions, which are lower in energy than σ-σ^* transitions. Nevertheless, isolated (nonconjugated) C=C double bonds still absorb below 200 mμ (for example, C_2H_4 at 162 mμ). In conjugated double-bond systems the energy of the π-π^* transition is less, so that absorption occurs at higher wavelengths. In general, the more con-

---

[8] Tsubomura, Kimura, Kaya, Tanaka, and Nagakura, *Bull. Chem. Soc. Japan* **37**, 417 (1964).

TABLE 1. Ultraviolet absorption of $CH_3—(CH=CH)_n—CH_3$ for some values of n[9]

n	mμ
2	227
3	263
6	352
9	413

jugation, the more the absorption is displaced toward higher wavelengths. An illustration of this rule is shown in Table 1.[9] When a chromophore absorbs at a certain wavelength, and the substitution of one group for another causes absorption at a higher wavelength, a *bathochromic shift* is said to have occurred. The opposite kind of shift is called *hypsochromic.* A bathochromic shift in the visible region causes the absorption to change in the order violet → blue → green → yellow → orange → red. Since the color we see is the complement of the absorbed light, a bathochromic shift in the visible causes the color to shift in the order yellow → orange → red → violet → blue → green.[10] A shift in this direction is defined as a *deepening* of color.

If one of the double-bond atoms possesses an unshared pair, then n-π^* transitions as well as π-π^* transitions are possible. Such groups (for example, C=O, C=N) absorb in regions where they are easily measurable (for example, cyclohexanone at 283 mμ). In such cases the spectrum often exhibits several peaks. For example, carbonyl groups give two peaks due to n-π^* transitions (a very weak one near 400 and a weak one near 290 mμ); a moderately strong peak due to an n-σ^* transition (about 180 mμ); and an intense peak caused by a π-π^* absorption (about 160 mμ).

Uses of Electronic Spectra. Since many compounds are transparent above 200 mμ, and chromophores absorb at positions which are not greatly sensitive to changes in molecular structure, ultraviolet data are usually not as useful as infrared or nuclear-magnetic-resonance data. Nevertheless, many valuable things may be learned if the structure of the material is suitable.

1. *Structure of unknown compounds.* One of the most important uses of electronic spectra is to determine the presence or absence of a given chromophore. The presence of an absorption peak where the chromophore is known to absorb is usually good evidence that the unknown contains such a group, though it is not conclusive, because other groups may absorb there too. However, the absence of a peak where it is expected may be regarded as fairly strong evidence that the chromophore is *not* present. The more complicated the molecule, the more peaks, and the more difficult it is to in-

---

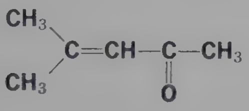
[9] Bohlmann and Mannhardt, *Chem. Ber.* **89,** 1307 (1956).

[10] For reviews on color and constitution, see Maccoll, *Quart. Rev.* (*London*) **1,** 16–58 (1947); Kuhn, *Fortschr. Chem. org. Naturstoffe* **16,** 169–205 (1958), **17,** 404–451 (1959).

TABLE 2. Absorption of some alkenes[11]

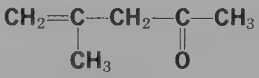
Alkene type	*mμ*
1-Alkenes	175
2-Alkyl-1-alkenes	187
cis-2-Alkenes	176
trans-2-Alkenes	179

terpret the spectrum. If the number of possibilities is limited, ultraviolet evidence may be conclusive. For example, the self-condensation product of acetone consists of two isomers, which, by other evidence, must be **1** and **2**.



1

and



$CH_2{=}C(CH_3){-}CH_2{-}C(=O){-}CH_3$

2

Ultraviolet spectra immediately tell which is which, since one is conjugated and the other is not.

A limited amount of additional structural information may often be obtained by making use of the shifts caused by group substitution. Table 2 gives absorption peaks of some simple alkenes.[11] As seen in the table, the type of alkene may be determined from the position of the peak, although the identity of individual alkenes cannot be determined, since, for example, 1-butene gives the same peak as 1-pentene. The fact that alkyl substitution causes a bathochromic shift of the C=C double-bond absorption has been interpreted as evidence for hyperconjugation.

2. *Identification of unknown compounds.* If the structure of an unknown compound is suspected, it is possible to compare the electronic spectrum of the unknown and of the known (if a sample of the known is available). Barring the effect of impurities, these spectra should coincide. If they do, as we have seen, this is not conclusive evidence for the structure, but if they do not, the supposed structure is incorrect. If the known is not available, it may be possible to find the spectrum in the literature.[12]

3. *Quantitative analysis.* The percentage of a compound in a mixture may

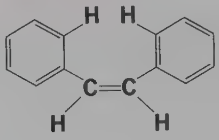
---

[11] Jones and Taylor, *Anal. Chem.* **27**, 228 (1955).

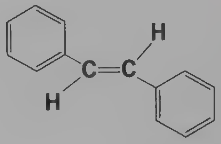
[12] The most extensive list of spectral peaks is given in "Organic Electronic Spectral Data," Interscience Publishers, Inc., New York. Four volumes have so far appeared, covering spectra which have appeared in the literature through 1959. Hershenson, "Ultraviolet and Visible Absorption Spectra," 2 vols., Academic Press Inc., New York, which also to date covers the literature through 1959, does not list peaks but gives compounds and the literature references for them. Landolt-Börnstein, "Zahlenwerte und Funktionen," Band I, teil 3, Mol. II, pp. 61–358, lists peaks and gives curves for many compounds. Spectra are also given in two loose-leaf publications, "Ultraviolet Spectral Data," American Petroleum Institute Research Project 44, begun 1945; and Láng, "Absorption Spectra in the Ultraviolet and Visible Region," Academic Press Inc., New York, begun in 1961. These are all compilations of data. For books which list data and discuss interpretations, see Gillam and Stern, Ref. 6, Jaffé and Orchin, Ref. 6, and Dyer, Ref. 5.

be determined if a sample of the pure compound is available, by measurement of peak heights.

4. *Determination of configurations of geometrical isomers.*[13] Table 2 shows that the absorption wavelength of *cis*-2-alkenes is slightly different from that of *trans*-2-alkenes. Correlations of this type have been made in several other cases. Such measurements are particularly useful where one of the isomers is forced to be noncoplanar by steric hindrance. This decreases resonance and results in absorption at lower wavelengths. Thus *cis*-stilbene (**3**) absorbs at 280 mμ, and the trans isomer (**4**) at 295.5 mμ.



3



4

5. *Determination of equilibrium constants.* In tautomeric systems and in other equilibria, the two forms of the compound often absorb at different positions. Quantitative analysis of each component can give equilibrium concentrations and hence equilibrium constants.

6. *Detection and study of molecular association.* It was mentioned in Chapter 3 that charge-transfer complexes are recognized by the formation of new spectral peaks. Information about the type of bonding involved may be obtained from a study of the effect of conditions on the position and intensity of these peaks.

7. Impurities may be detected, even in compounds which do not themselves absorb, as long as the impurity absorbs.

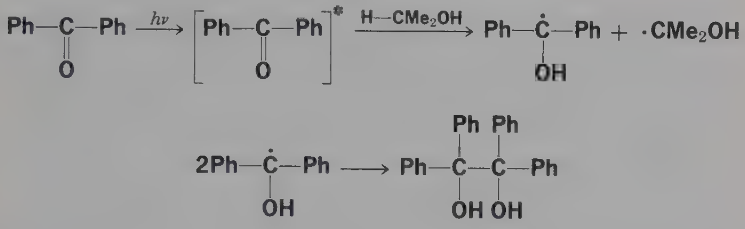
8. Ultraviolet spectra are often used for rate studies and for detection of intermediates in reactions. This will be discussed in Chapter 7.

In addition to these uses, physical chemists obtain much useful information about the excited states of molecules and energy transitions between states.

The Fate of the Excited Molecule. We shall briefly discuss what happens to a molecule after it has had an electron promoted to an orbital of higher energy. The molecule may give up the excess energy and drop back to the lower level. If this happens, the energy is given off in the form of heat or light, the latter being known as *fluorescence*. However, in some cases, instead of dropping back, the molecule disintegrates. Disintegration into free radicals is frequently caused by ultraviolet light, and this is known as *photolysis*. Ionic dissociation usually requires light of very high energy: below 180 mμ. Dissociation is aided by the *Franck-Condon principle,* which states that the promotion of an electron takes place much faster than a single vibration. As shown in Figure 2, the equilibrium distances are greater in the excited state than in the ground state. When a molecule is suddenly promoted, it is in a compressed condition, which may be relieved by an outward surge which is sufficient to dissociate the bond. Aside from dissociation of a covalent bond, the excited molecule may undergo other reactions which are not characteristic of the ground-state molecule. For example, when benzophenone is excited in the presence of isopropyl alcohol, it abstracts a hydrogen atom to give a free radical which dimerizes:

---

[13] For a review of the relationship between spectra and structure, see Braude and Waight, *Progr. Stereochem.* **1**, 126–177 (1954).



$$\mathrm{Ph{-}\underset{\underset{O}{\|}}{C}{-}Ph} \xrightarrow{h\nu} \left[\mathrm{Ph{-}\underset{\underset{O}{\|}}{C}{-}Ph}\right]^{*} \xrightarrow{\mathrm{H{-}CMe_2OH}} \mathrm{Ph{-}\underset{\underset{OH}{|}}{\dot{C}}{-}Ph} + \cdot\mathrm{CMe_2OH}$$

$$\mathrm{2Ph{-}\underset{\underset{OH}{|}}{\dot{C}}{-}Ph} \longrightarrow \mathrm{Ph{-}\overset{\overset{Ph}{|}}{\underset{\underset{OH}{|}}{C}}{-}\overset{\overset{Ph}{|}}{\underset{\underset{OH}{|}}{C}}{-}Ph}$$

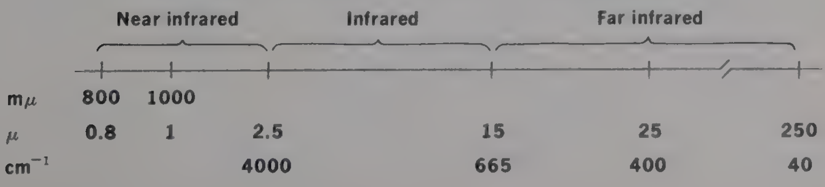
Another type of reaction which may occur upon excitation is cis-trans isomerization. For example, *trans*-stilbene may be converted to *cis*-stilbene by irradiation in the presence of a photosensitizer. In some cases reaction is undergone by both the ground-state molecule and the excited state, but the stereochemical results are different (see p. 841). The study of reactions undergone by excited states of molecules is called *photochemistry.*

Infrared Spectroscopy.[14] Transitions occur not only between one electronic level and another, but also between one rotational or vibrational level and another within an electronic level. The energy of these transitions is of course much less (Figure 2) and corresponds to light in the infrared region. Vibrational transitions are found in the infrared and the near infrared. Purely rotational transitions are in the far infrared (see Figure 4) and micro-

---

[14] For books on infrared spectra and their interpretation, see Bellamy, "The Infrared Spectra of Complex Molecules," 2d ed., John Wiley & Sons, Inc., New York, 1958; Cross, "An Introduction to Practical Infrared Spectroscopy," 2d ed., Butterworth & Co. (Publishers), Ltd., London, 1964; and Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, 1962. The latter book contains 85 spectra as problems. The solution of these problems will give the student a large amount of competence in the interpretation of infrared spectra. Infrared spectra are discussed in the Weissberger series (see Ref. 5) by Anderson, Woodall, and West, vol. I, part 3, pp. 1959–2019; Duncan, vol. IX, pp. 187–246; Jones and Sandorfy, vol. IX, pp. 247–580; and Cole, vol. XI, pp. 133–174; and in "Determination of Organic Structures by Physical Methods" (see Ref. 5) by Gore, vol. 1, pp. 195–219; and Wilson, vol. 2, pp. 181–243. For other review articles see Sheppard and Simpson, *Quart. Rev. (London)* **6**, 1–33 (1952), **7**, 19–55 (1953); Wheeler, *Chem. Rev.* **59**, 629–666 (1959) (near infrared); and Wood, *Quart. Rev. (London)* **17**, 362–381 (1963) (far infrared).

Figure 4. *The infrared region of the spectrum.*



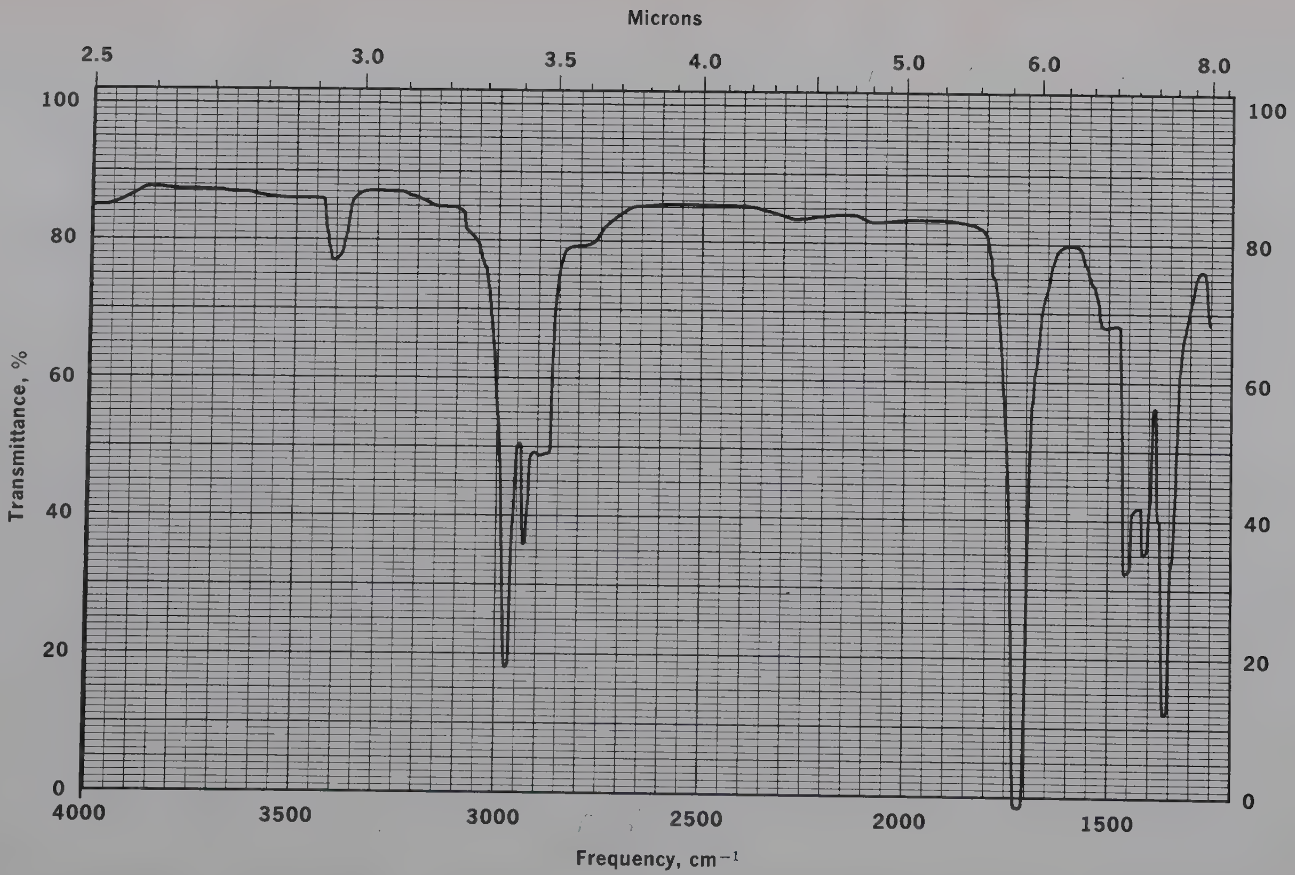


Figure 5. *Infrared spectrum of methyl ethyl ketone.*

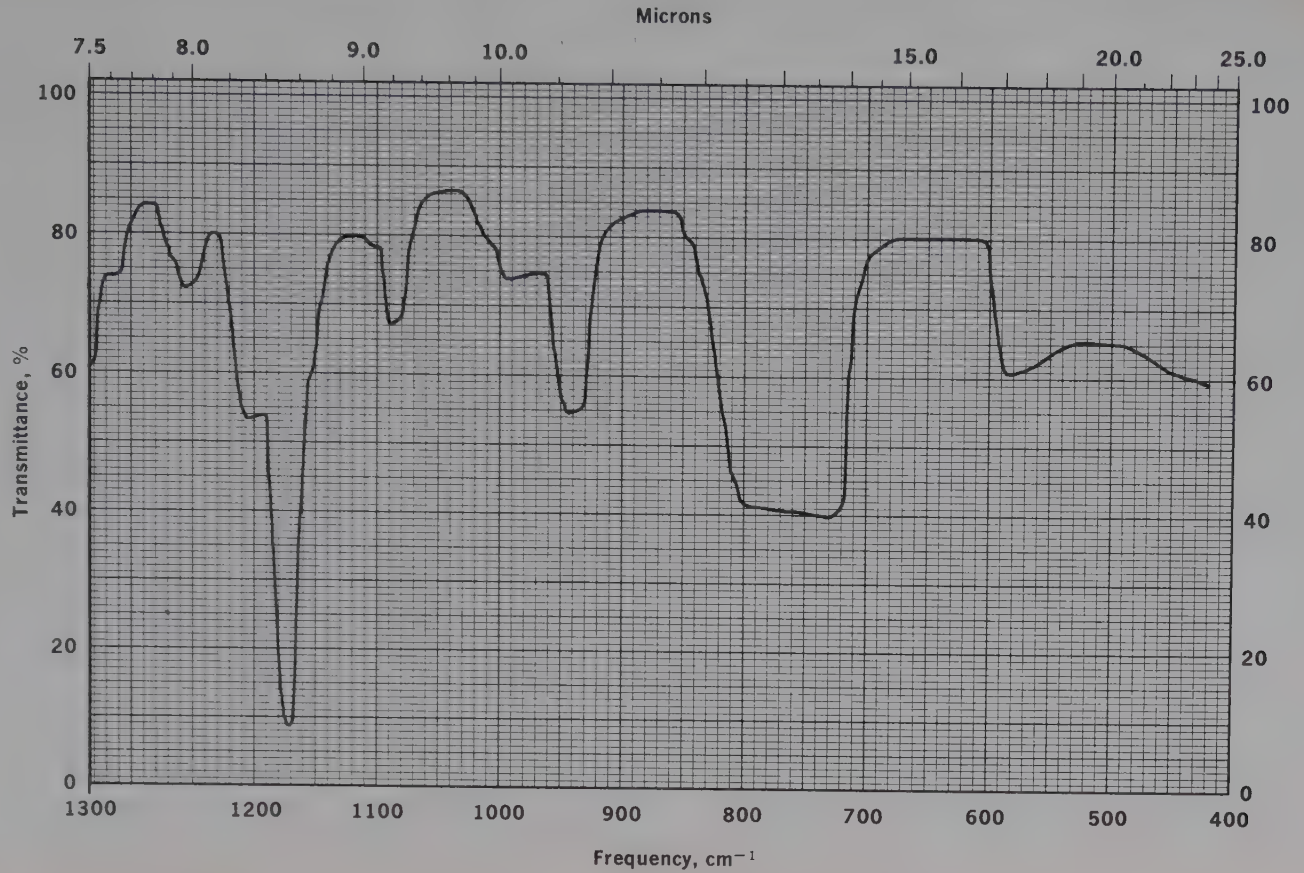


Figure 5. *(Continued.)*

wave regions of the spectrum. Standard infrared spectrophotometers, available to most organic chemists, cover the region from 2.5 to 15 or 25 μ. Partly owing to a lack of good instrumentation, but also because of the inherently smaller usefulness of the data, near and far infrared measurements are much less often made. Infrared spectra are more complex than electronic spectra (compare Figures 5 and 3), and nonrecording instruments are not practical. Some commercial instruments plot the absorption against a linear change in wavelength, but others linearly change the *wave number*. The wave number, the units of which are cm^{-1}, is the reciprocal of the wavelength, expressed in centimeters. Wave-number measurements are usually preferred, because they are proportional to energy.

Molecules may vibrate in several ways. The more atoms in a molecule, the more modes of vibration it possesses. One type of vibration, called *stretching*, occurs between two atoms directly bonded, and resembles the vibrations of a spring. These vibrations give rise to peaks which are characteristic of the bond and which are always found in about the same place for a given bond no matter what the rest of the molecule contains. For example, compounds containing O—H bonds exhibit a peak between 2.7 and 3.4 μ (3700 to 3000 cm^{-1}). The positions of stretching peaks are dependent on the strength of the bond and on the mass of the atoms directly connected. The stretching frequencies for single bonds containing hydrogen appear at the lowest wavelengths (about 2.5 to 3.6 μ, or 4000 to 2800 cm^{-1}). When hydrogen is replaced by deuterium, the mass of the atom is doubled, and the stretching frequencies are displaced toward higher wavelengths. For example, the stretching frequency of C—D bonds is about 4 to 5 μ. Single bonds between atoms of higher mass (C—C, C—O, C—S, etc.) absorb between 6.7 and 15 μ (1500 to 650 cm^{-1}). Double bonds are stronger than single bonds and have stretching frequencies at lower wavelengths; triple bonds are found lower still. The double-bond-stretching region is about 5.2 to 6.7 μ (1900 to 1500 cm^{-1}), and the triple-bond (and allene) region is about 4.2 to 5.0 μ (2400 to 2000 cm^{-1}). Besides the stretching frequencies, there are also bending, twisting, scissoring, and other kinds of vibrations. These are functions of three nonlinear atoms and occur at wavelengths above about 6.2 μ (1600 cm^{-1}).

The infrared region may be divided roughly into two parts. The section from 2.5 to about 6.7 μ (4000 to 1500 cm^{-1}) contains peaks which are characteristic of individual groups. Double and triple bonds and single bonds of hydrogen or deuterium cause peaks whose position is only slightly changed by the rest of the molecule. This area may be used for identification of groups. The portion of the spectrum from about 6.7 to 15 μ (1500 to 650 cm^{-1}) is more complicated. Both stretching and other kinds of vibrations appear in this area, and single bonds which do not contain hydrogen or deuterium appear over a wider area than those which do. This region is much less often used to search for characteristic peaks, but it is known as the *fingerprint region* of the spectrum, since each compound has a different spectrum in this area. Even in this region, however, careful study by a trained investigator will often be able to identify the source of most of the peaks, if the structure is known.

The ultraviolet-visible region is transparent to many organic compounds; in contrast, all organic compounds (and most inorganic compounds) absorb in the infrared. The only requirement for absorption in this region is that a vibrational transition be available such that the dipole moment of the molecule is different in the two vibrational states. This brings up the problem of what to hold the sample in, since the container (at least that part of it through which the light passes) must be transparent to infrared radiation if a spectrum is to be recorded. In practice most cells designed to hold gases, liquids, or solutions are constructed with windows of sodium chloride, which is transparent in this range. Solids are frequently powdered, mixed with potassium bromide, and pressed into pellets. Solutions present a special problem, since all solvents absorb in the infrared region. For this reason, commercial instruments are double-beam: that is, the spectrum of the solution and the solvent are simultaneously recorded, and the latter automatically subtracted from the former. Of course, water cannot be used as a solvent in a sodium chloride cell.

Uses of Infrared Spectroscopy. Because a typical infrared spectrum contains much more information than the electronic spectrum of the same molecule, it is usually much more useful.

1. *Structure of unknown compounds.* As with electronic spectra, the presence or absence of a characteristic peak may be used as evidence for the presence or absence of the corresponding group. However, the infrared spectrum is more valuable than the electronic because many more groups characteristically absorb in the infrared. Aside from detection of a given functional group, other information about the structure may often be obtained. Changes in the structure of a molecule cause slight changes in the position of peaks, in a way that can be predicted. For example, not only does the presence of a peak at about 5.2 to 6.2 μ (1900 to 1600 cm^{-1}) indicate that the C=O group is present, but the actual position of the peak within this range tells a good deal about the rest of the molecule. Table 3 lists the stretching frequencies of some types of carbonyl compounds.[15] The shifts in frequency are caused by factors which affect the strength of the bond. Thus, conjugation with another double bond shifts the C=O stretching frequency to higher wavelengths (Table 3) because the bond is weakened by removal of some of the electron density.

2. *Identification of unknown compounds.* Since the total infrared spectrum of a molecule is characteristic of it alone, the spectrum may be regarded as a fingerprint. No two compounds have the same infrared spectrum unless they are enantiomers. This means that, if the structure of an unknown compound is suspected and if a sample of the compound or a copy of its spectrum can be obtained, then a fairly positive identification may be made by overlapping the spectra. Barring the effect of impurities, if two spectra fail to overlap, they are of different molecules, but if they overlap, it is fairly cer-

---

[15] Bellamy, Ref. 14.

TABLE 3. C=O stretching frequencies in various types of compounds[15]

Type of carbonyl compound	*Peak, cm^{-1}*
Saturated open-chain ketones	1725–1705
α,β-Unsaturated ketones	1685–1665
Monoaryl ketones	1700–1680
Diaryl ketones	1670–1660
Cyclohexanones	1725–1705
Cyclopentanones	1750–1740
Cyclobutanones	1775–1780
Saturated aldehydes	1740–1720
α,β-Unsaturated aldehydes	1705–1680
Aromatic aldehydes	1715–1695
Saturated aliphatic acids	1725–1700
Carboxylate ions	1610–1550
Acyl halides	1815–1770
Open-chain anhydrides	1850–1800
Saturated open-chain esters	1750–1735
Saturated γ-lactones	1780–1760
Unsubstituted amides	1690–1650

tain that the compounds are the same.[16] The controversial drug Krebiozen was reported to be identical to the common biological compound creatine on the basis of its infrared spectrum.

3. *Detection of hydrogen bonding.*[17] Infrared frequencies of groups such as O—H or C=O are shifted when the group is hydrogen-bonded. Hydrogen bonding always moves the peak toward higher wavelengths, for both the donor and the acceptor groups, although the shift is greater for the former. For example, a free OH group absorbs at about 3600 to 3650 cm^{-1}, while a hydrogen-bonded OH group is found about 50 to 100 cm^{-1} lower, at 3500 to 3600 cm^{-1}.[18] In many cases there is partial hydrogen bonding (that is, some OH groups are free and some are hydrogen-bonded). In such cases two peaks appear. Infrared spectroscopy can also distinguish between inter- and intramolecular hydrogen bonding, since intermolecular peaks are intensified

---

[16] Compilations of infrared spectra are issued in loose-leaf or card form by the American Petroleum Institute Research Project 44; Samuel P. Sadtler and Son, Philadelphia, Pa.; and by a number of other sources. Many spectra are given in Randall, Fowler, Fuson, and Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Company, Inc., Princeton, N.J., 1949. The preceding book; Bellamy, Ref. 14; Nakanishi, Ref. 14; and Cross, Ref. 14, contain many tables of peak attributions. Infrared peaks and spectra are given in Landolt-Börnstein, "Zahlenwerte und Funktionen," Band I, teil 2, Mol. I, pp. 328–551, while pp. 39–211 of this volume lists literature references where infrared, Raman, and microwave data may be found for specific compounds. Hershenson, "Infrared Absorption Spectra," Academic Press Inc., New York, 1959–1964, lists, for the period 1945–1962, literature references for infrared spectra of many compounds. Szymanski, "Infrared Band Handbook," Plenum Press, New York, 1963, with supplements, lists infrared peaks in numerical order and gives one or more compounds which absorb at each peak.

[17] For a review, see Tichý, *Advan. Org. Chem.* **5**, 115–298 (1965).

[18] Reference 17 contains a lengthy table of free and intramolecularly hydrogen-bonded peaks.

by an increase in concentration, while intramolecular peaks are unaffected.

4. *Determination of configuration.* Each conformer has its own infrared spectrum, and the peak positions are often different. For example, the C—F bond in equatorial fluorocyclohexane absorbs at 1062 cm^{-1}, while the axial C—F bond absorbs at 1129 cm^{-1}.[19] Many relationships of this kind are known, and it is often possible to tell which conformation a molecule has, and for mixtures, what percentage is in each conformation. Because of the relationship between configuration and conformation in cyclic compounds (see p. 106), configuration may frequently be determined too.

5. *Determination of bond distances and angles.* The frequencies of the absorption peaks in a molecule are related to the force constants of the vibrations. For simple molecules, these force constants may be determined from the frequencies, and then used to calculate bond distances and angles.

In addition to these uses, infrared peaks may be used in the same way as ultraviolet peaks for quantitative analysis, determination of configurations of geometrical isomers, determination of equilibrium constants, detection of impurities, rate studies, and detection of intermediates.

Other Kinds of Spectra. Two other spectral methods, which are much less often used by organic chemists but from which useful information may be obtained, are *Raman* and *microwave spectra.*

Raman spectra[20] cover the same spectral range as infrared spectra but are obtained in a completely different way. A beam of monochromatic light is sent into a liquid sample. The light is of a frequency that is *not* absorbed by the molecule (most often 4358 Å from a mercury arc). That portion of the light which scatters at right angles is then examined, and it is found that a series of lines appears (Figure 6).[21] The incident frequency is taken as zero, and the lines are measured in cm^{-1} from this position. The Raman spectrum is different for each compound, and thus provides another fingerprint. In

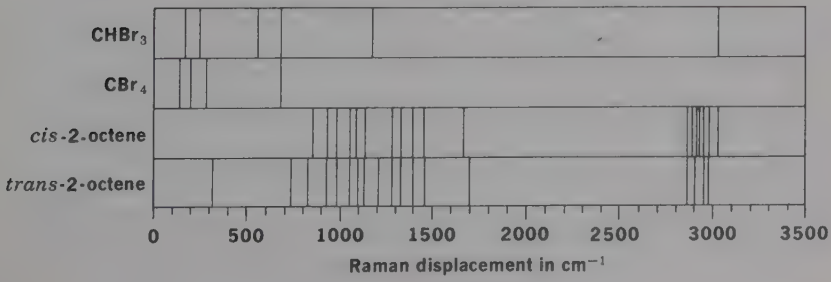
---

[19] Larnaudie, *Compt. rend.* **235,** 154 (1952).

[20] For reviews see Cleveland, in Braude and Nachod, "Determination of Organic Structures by Physical Methods," vol. 1, pp. 231–258, Academic Press Inc., New York, 1955; and Sushchinskii, *Spectrochim. Acta* **14,** 271–283 (1959). The subject is also treated by Duncan, Ref. 14, and by Jones and Sandorfy, Ref. 14.

[21] Taken from Cleveland, Ref. 20, p. 235.

Figure 6. *Raman spectra of some compounds.*[21]



addition, groups appear at positions which are unchanged from one compound to another. For example, the C—H line appears at 3000 cm^{-1} and the C=C line at 1700. For simple molecules Raman spectra may be calculated from structural considerations. In these cases the structure of an unknown compound may be determined by comparison of the actual spectrum with the calculated one.

The Raman method is complementary to ordinary infrared spectroscopy, since some modes of vibration appear in one and not the other. Selection rules, which are based on the symmetry of the molecule, govern which modes of vibration appear and which do not appear, in each spectrum.[22] For example, for molecules with a center of symmetry, no mode of vibration which appears in the infrared spectrum is allowed in the Raman, and vice versa. It was mentioned earlier that vibrational transitions which do not change the dipole moment do not appear in the infrared spectrum. Therefore these vibrations are allowed in the Raman spectrum. For molecules with no symmetry, all of the vibrational modes are allowed in both the Raman and the infrared spectrum, although they may not all be strong enough to be observable.

The main reason that Raman spectra are measured much less often than infrared is that experimental difficulties are greater.

Microwave spectra[23] cover the region of wavelengths of 1000 μ (1 mm) and above, ranging to many kilometers, or as far as detectable. The method is greatly limited, being applicable only to gases at low pressures (0.001 to 0.1 mm Hg) and only to compounds with dipole moments. Only pure rotational transitions are found in this region, and the peaks do not overlap. However, the peaks are not characteristic of groups within a molecule. Microwave spectra are chiefly useful for providing information about the size and shape of molecules. Rotational levels are dependent on moments of inertia, which can be calculated from the positions of the peaks. From these, bond distances, angles, dipole moments, and rotational barriers may be calculated.

Nuclear Magnetic Resonance (nmr).[24] Certain nuclei possess an intrinsic spin, with a *spin number* (I) of $\frac{1}{2}$, 1, $\frac{3}{2}$, etc. A spin number of 0 means that the nucleus has no spin. A given nucleus has the same spin number in all environments. Since nuclei are charged, the spin gives rise to a magnetic field, and the nucleus behaves as a tiny magnet. If an external magnetic field is imposed, the nucleus aligns itself in this field. Each nucleus may take one of $2I + 1$ orientations, each of a given energy. The energy is quantized, and a transition between one of these orientations and another requires external energy.

---

[22] For a discussion, see Cleveland, Ref. 20, pp. 239–255.

[23] This subject is covered in the Weissberger series (see Ref. 5) by Dailey, vol. I, part 4, pp. 2635–2662; and by Gordy, vol. IX, pp. 71–186; and in "Determination of Organic Structures by Physical Methods" (see Ref. 5) by Wilson and Lide, vol. 1, pp. 503–524.

[24] For books on nuclear magnetic resonance, see Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, 1959; Pople, Schneider, and Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Company, New York, 1959; Roberts, "Nuclear Magnetic Resonance: Applications to Organic Chemistry," McGraw-Hill Book Company, New York, 1959; and Bhacca and Williams, "Applications of NMR Spectroscopy in Organic Chemistry; Illustrations from the Steroid Field," Holden-Day, San Francisco, 1964. This topic is discussed in the Weissberger series (see Ref. 5) by Gutowsky, vol. I, part 4, pp. 2663–2800, and by Stothers, vol. XI, pp. 175–260, and in "Determination of Organic Structures by Physical Methods" (see Ref. 5) by Phillips, vol. 2, pp. 401–463; Lauterbur, vol. 2, pp. 465–536; and Richards, vol. 2, pp. 537–562. Many review articles have been published, a few of which are: Conroy, *Advan. Org. Chem.* **2**, 265–328 (1960); Brownstein, *Chem. Rev.* **59**, 463–496 (1959); Gillespie and White, *Progr. Stereochem.* **3**, 53–92 (1962); and Katritzky, *Record Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) **23**, 223–241 (1962).

In organic chemistry by far the largest amount of attention has been paid to the ^1H nucleus, the proton, and the nmr of protons is often called *proton magnetic resonance.* For the proton, $I = \frac{1}{2}$, so that there are two possible orientations: the proton aligned with the field or (higher energy) against it. The amount of energy necessary to cause the proton to flip over so that it is oriented against the field is dependent on the strength of the external field and, for fields of the order of 10,000 to 100,000 gauss, corresponds to radiation of about 10 to 60 Mc/sec (long-wave radiation is usually measured in cycles per second; the wavelengths are of the order of 1 meter), which is in the radio-frequency region. The energy necessary to cause the jump is supplied by a radio-frequency oscillator which sends out a constant frequency. The magnetic field is slowly varied until at a certain field strength, the energy is just right, and the proton flips over. This is described as *resonance.*[25] Transitions can occur only at one value of the field strength for a given frequency. For a bare proton, at 10,000 gauss, the frequency is 42.57 Mc/sec. A radio-frequency detector is used to measure the signal after it leaves the sample and thus to detect the occurrence of the resonance. The process could be reversed: that is, the field strength could be held constant and the frequency varied, but the practice is to use the former method, since it is easier to make slight variations in magnetic strength than in frequency. Most instruments operate at 60 Mc/sec.

The entire value of nmr for organic chemistry lies in the fact that the field strength (at a given constant frequency) necessary for resonance is not the same for protons in different environments. A proton in a molecule is always shielded by electrons, in a different way for each nonequivalent proton, and the field "seen" by the proton is not the same as the field applied by the magnet. At a constant frequency, say 42.57 Mc/sec, each proton will flip over when the field that it "sees" reaches the right value, in this case 10,000 gauss, but differently shielded protons will "see" this field at different values of the applied field. Thus when the magnetic field is varied, signals will be recorded at separate places for each nonequivalent proton. The dependence of peak position on the environment of the proton is called *chemical shift,* because early investigators did not expect it. The variation of the total field necessary to flip all the protons is only about 10 ppm, so that accurate measurement is necessary.

An instructive example is the low-resolution spectrum of ethanol (Figure 7). There are three types of hydrogen atoms in this compound, and each has its own peak. An important fact is that the area under each peak is proportional to the number of equivalent hydrogens. This is one way

---

[25] The use of the word "resonance" to describe this phenomenon has no connection with its use in Chapter 2 (and throughout this book) to describe electron delocalization.

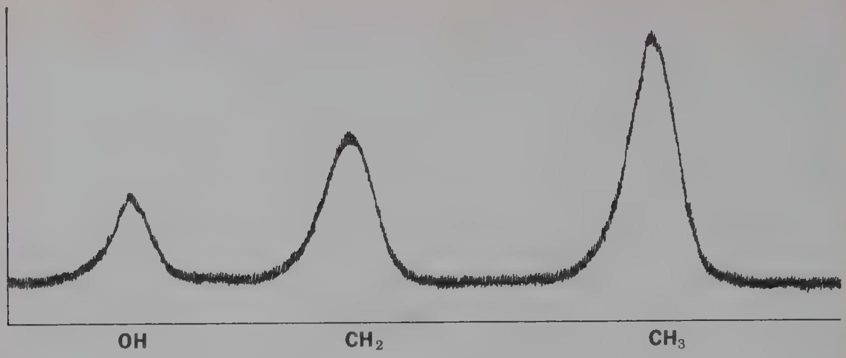
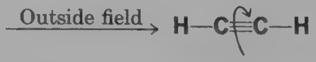


Figure 7. *Low-resolution nmr spectrum of ethanol.*

in which the peaks can be identified. The area ratio is 3:2:1, corresponding to CH_3, CH_2, and OH protons.

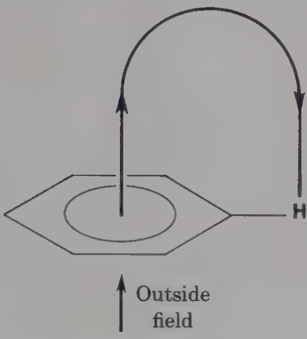
Shielding is caused by the fact that the electrons around the nucleus are caused to circulate by the applied field, producing a field of their own which is opposed to the external one. The nucleus thus receives a field which is of a lower intensity than the one applied. When no *magnetically anisotropic* group (that is, a group which is not equally magnetized along all three axes) is present, then the greater the electron density, the lower the field strength felt by the nucleus. Since the position of the peak is directly related to the field strength felt by the nucleus, this becomes a way of measuring electron density, and hence electronegativity, since the electronegativity of an atom attached to hydrogen generally determines the electron density on the hydrogen.

However, when a magnetically anisotropic group is present, then the relationship no longer applies. A triple bond, for example, has different electron circulation depending on whether it is aligned parallel or perpendicular to the applied field. If the triple bond is parallel to the field, then the π electrons circulate around the triple bond



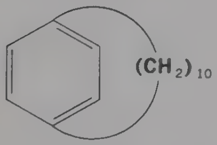
and send out a field which is against the applied field, subtracting from it and shielding the protons in a way that has nothing to do with electronegativity. If the triple bond is perpendicular to the field, there is no motion of the electrons, and the triple bond does not contribute to the shielding. In a liquid or a gas, the molecules are randomly oriented, and each triple bond shields its protons to the extent that it is aligned parallel to the field, and the net effect is shielding. If we expected the normal relationship between electron density and peak position to determine the position of the C—H peak of acetylene, we would find the peak in the "wrong" place, since acetylenic protons have lower electron densities than most C—H protons.

Another magnetically anisotropic group is an aromatic ring, which has a closed loop of electrons. In benzene, for example, the outside field perpendicular to the plane of the ring sets up a ring current, which in turn causes an induced field, which, at the protons, is parallel to the main field:



This is a *deshielding* effect, since the field "seen" by the protons is increased. However, if there were protons directly above the ring, *they* would be shielded. The nmr spectrum of **5** showed that this was the case[26] and that the CH_2 peaks were shifted to higher τ, the closer they were to the middle of the chain.[27]

An nmr instrument does not indicate absolute line positions, as do electronic and infrared spectrophotometers. What are obtained are simply the peaks. To make these useful, it is necessary to have values attached to them. Two things are done to achieve this end. First, a standard compound is run along with the sample. The most common is tetramethylsilane, which has only one peak. The standard may be external to the sample or mixed with



5

it if the two materials do not interact. An arbitrary value of zero is given to the single peak produced by the standard. Second, it is necessary to tell how far the peaks of the sample are from that of the standard, and from each other. There are several ways of doing this, but the most common is the sideband technique, which consists of superimposing a signal of known frequency (say 100 cycles/sec) on the reference peak. Lines then appear on the spectrum at these distances, and the peaks may be calibrated. However, the amount of chemical shift depends on the frequency, and any frequency may be used; hence a way of *expressing* peaks for comparison purposes is required. For this, the value δ is defined:

$$\delta = \frac{\Delta \times 10^6}{\text{oscillator frequency (cycles/sec)}}$$

---

[26] Waugh and Fessenden, *J. Am. Chem. Soc.* **79**, 846 (1957).

[27] Increased shielding shifts the position of peaks to lower τ values (downfield), and increased deshielding shifts them to higher τ values (upfield). See page 186 for the meaning of τ.

where Δ is the distance in cycles per second between the peak and the reference, Δ being taken as negative if the peak is at a lower frequency than the reference. The value δ, which is dimensionless and expressed in parts per million (ppm), is also equal to

$$\frac{H_s - H_r}{H_r}$$

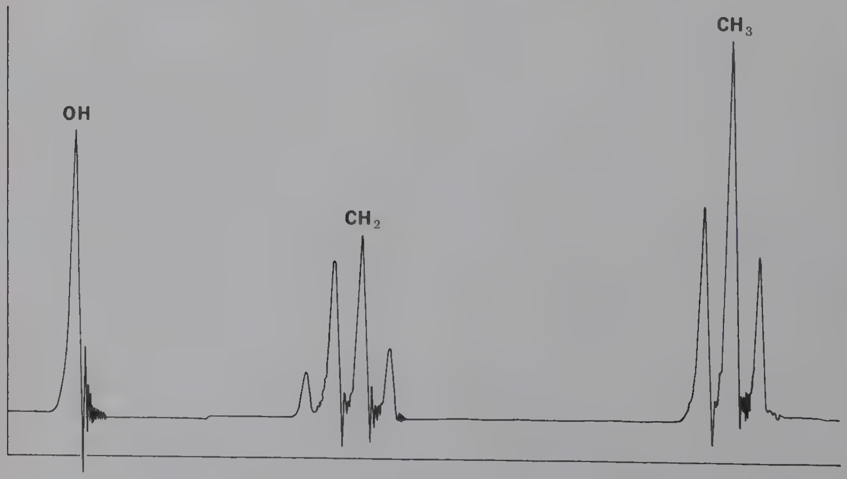
where H_s is the field strength of the peak, and H_r that of the reference. Since δ for most peaks is negative, τ, which is equal to $10 + \delta$, is often used.

In Figure 7 were shown the three peaks of the ethanol spectrum. When higher resolution is used, it is seen that two of these peaks are split, although the total areas under the peaks are unchanged (Figure 8). The splitting, from which much useful information may be obtained, is caused by coupling between nonequivalent protons. The field experienced by the CH_3 protons is influenced by the spins of the protons on the adjacent carbon, in this case CH_2. In any individual molecule, the two CH_2 protons may be aligned in three ways: (*a*) both protons aligned with the field, (*b*) both aligned against the field, or (*c*) one aligned with it and one against it:

$$\begin{array}{ccccc} \uparrow\uparrow & & \uparrow\downarrow & & \downarrow\downarrow \\ & & \downarrow\uparrow & & \\ (a) & & (c) & & (b) \\ 1 & : & 2 & : & 1 \end{array}$$

The laws of probability predict that about one-fourth of the molecules will have the two CH_2 protons in alignment (*a*), about one-fourth in alignment

Figure 8. *High-resolution nmr spectrum of ethanol.*



(*b*), and one-half in alignment (*c*). Any particular CH_3 will thus have a 25% chance of being influenced by alignment (*a*), a 25% chance of being influenced by alignment (*b*), and a 50% chance of being influenced by alignment (*c*). The CH_3 peak is therefore split into three parts, in the ratio 1:2:1, each part being due to a fraction of the molecules present. Similarly protons on a carbon next to a single CH group will give rise to a doublet peak which shows a 1:1 split, and protons with no hydrogens on adjacent atoms will produce unsplit peaks. The CH_2 peak in ethanol is split into four parts in a 1:3:3:1 ratio, since the protons on the carbon adjacent to *it* can be aligned in four ways:

↑↑↑		↑↑↓		↓↓↑		↓↓↓
		↑↓↑		↓↑↓		
		↓↑↑		↑↓↓		
1	:	3	:	3	:	1

These interactions, called *spin-spin coupling,* are independent of the strength of the applied field, so that, although chemical shifts change with field strength, the spacing between the parts of a split peak does not. The spacing between two parts of a split peak is known as the *coupling constant J,* usually expressed in cycles per second.[28] No splitting is caused by interaction between equivalent protons, so that the three protons of a methyl group do not split each other, and ethane and benzene, for example, both have only one unsplit peak. As a general rule there is coupling only between protons of adjacent atoms (that is, across no more than three bonds), though longer coupling has been observed in some conjugated systems and even, in special cases, in nonconjugated systems.[29] Spin-spin coupling, while quite useful, can be difficult to interpret in complex systems, where the splitting pattern may be very complicated.[30] Also, in complex compounds, the distance J is often of the same order of magnitude as the chemical shift, which causes further difficulties in interpretation, for two reasons: (1) It is not always easy to tell a true peak from one that is merely a part of another peak, and (2) second-order interactions arise, further complicating the spectra. Two ways to overcome this particular difficulty are by massive deuteration, in which case the chances of a proton's being adjacent to another are decreased,[31] and by *nuclear magnetic double resonance,* in which decoupling is achieved by simultaneously imposing two radio-frequency waves of different frequencies.[32] Another expedient is running two complete spectra at different field strengths. Splitting can be distinguished from chemical shifts, since chemical shifts change with field strength, but J values do not. To this end, instruments which operate at 100 Mc/sec are commercially available.

---

[28] For a discussion of coupling constants, see Muller, *Bull. Soc. chim. France* **1964,** 2027–2032.

[29] See, for example, Meinwald and Lewis, *J. Am. Chem. Soc.* **83,** 2769 (1961); Davis, Lutz, and Roberts, *J. Am. Chem. Soc.* **83,** 246 (1961); Musher and Corey, *Tetrahedron* **18,** 791 (1962); Gagnaire and Payo-Subiza, *Bull. Soc. chim. France* **1963,** 2623, 2627; Karabatsos, Taller, and Vane, *Tetrahedron Letters* **1964,** 1081; Martin-Smith, Reid, and Sternhell, *Tetrahedron Letters* **1965,** 2393. For a review, see Sternhell, *Rev. Pure Appl. Chem.* **14,** 15 (1964). For a theoretical treatment, see Barfield, *J. Chem. Phys.* **41,** 3825 (1964).

[30] For a monograph, see Roberts, "An Introduction to the Analysis of Spin-Spin Splitting in High Resolution Nuclear Magnetic Resonance," W. A. Benjamin, New York, 1961. For charts of spectra, calculated for many possible coupling situations, see Wiberg and Nist, "The Interpretation of NMR Spectra," W. A. Benjamin, New York, 1962. For a brief treatment, see Becker, *J. Chem. Educ.* **42,** 591–596 (1965).

[31] Garnett, Henderson, Sollich, and Tiers, *Tetrahedron Letters* **1961,** 516.

From the foregoing considerations, the reader may be wondering why the OH peak in Figure 8 was not split, since it is adjacent to a CH_2 group. The reason is that the OH proton does not remain on one oxygen but rapidly shifts back and forth among many. Thus a given OH proton, within a very short time, may be on an oxygen adjacent to a CH_2 with both protons aligned with the field (↑↑), then on a molecule in which the CH_2 has both protons against the field (↓↓), etc. Within this time it will be on many oxygen atoms, and the spectrum shows only an unsplit peak which is the average of the three peaks which would be there if the protons did not wander. The rapid proton transfer in ethanol is catalyzed by traces of acid or base, and if the ethanol is rigorously purified, the OH peak is indeed found split into three parts (and the CH_2 into eight). This introduces another aspect of proton magnetic resonance: there is a time factor. If any change occurs in the environment of the proton faster than about 10^3 changes per second, the nmr spectrum shows only an average peak. If the changes are slower, then both peaks (or more than two) would be found, in proportion to the concentrations.

We may briefly consider other nuclei. Nuclei with spin numbers of 0 give no signals and are useless in nmr. Some nuclei which fall into this class are important in organic chemistry: ^{12}C, ^{16}O, ^{18}O, ^{28}Si, ^{30}Si, ^{32}S, and ^{34}S. Nuclei with spin numbers of $\frac{1}{2}$ behave like the proton but do not interfere with the proton spectrum, because, at a given frequency, they absorb at field strengths which are relatively far away. However, they may couple with protons and cause proton peaks to split. Much useful information is obtained from nmr of these nuclei: ^{3}H, ^{13}C, ^{15}N, ^{19}F, ^{29}Si, and ^{31}P, and the principles are similar to those of proton magnetic resonance.[33] Nuclei with spin numbers of 1 or more have more than two possible alignments and exhibit *nuclear quadrupole resonance* (see p. 195). Among the nuclei in this class are ^{2}H, ^{14}N, ^{17}O, ^{33}S, ^{35}Cl, ^{79}Br, ^{81}Br, and ^{127}I. These nuclei give nmr spectra,[34] but the peaks are broader and the spectra less useful for identification than are those from nuclei with spin numbers of $\frac{1}{2}$.

Uses of Nuclear Magnetic Resonance. Nmr has been used by organic chemists for a shorter time than ultraviolet or infrared spectroscopy, but in that time it has developed into a highly important technique. Some of its applications are discussed below.

1. *Structure of unknown compounds.* Several aspects of the nmr spectrum are helpful for this purpose. Protons in similar environments have similar

---

[32] For reviews of this technique, see Baldeschwieler and Randall, *Chem. Rev.* **63,** 81–110 (1963); and Parello, *Bull. Soc. chim. France* **1964,** 2033–2062.

[33] For a review of ^{13}C nmr, see Stothers, *Quart. Rev.* (*London*) **19,** 144–167 (1965).

[34] For a discussion of nmr of deuterium compounds, see Diehl and Leipert, *Helv. Chim. Acta* **47,** 545 (1964).

TABLE 4. τ values for some methyl protons[36]

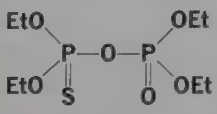
Compound	τ
$CH_3—CH_3$	9.12
$CH_3—CH_2Cl$	8.50
$CH_3—Cl$	6.95
$CH_3—OH$	6.62
$CH_3—CHO$	7.83

chemical shifts (τ or δ values). For example, methyl groups in alkanes are found at $\tau \approx 9$, aromatic hydrogens at $\tau \approx 2$ to 3, aldehydic hydrogens at $\tau \approx 0$ to 0.5, etc.[35] However, chemical shifts are more dependent on the rest of the molecule than are infrared or ultraviolet peaks. Table 4 lists chemical shifts for the methyl protons of various molecules.[36] Because of this variation, a larger number of standard values is required for peak assignment. However, with the help of other data, it is often relatively simple to make such assignments.

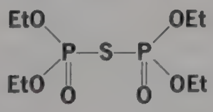
Spin-spin splitting often gives much molecular information, since if the spectrum can be fully analyzed, it tells how many protons are on each carbon adjacent to any atom bearing one or more protons. Again this is most useful when the number of structural possibilities is limited.

An important piece of information derived from the nmr spectrum is the number of hydrogens of each different type. In favorable cases it is possible to determine the total number of hydrogens in the molecule. Modern instruments are equipped with automatic integrators, which plot the number of hydrogens responsible for each peak.

Further information may be obtained from resonance of other nuclei. Interpretation of these spectra is usually far simpler, since there are not many (often only one) of the proper nuclei present. For example, the study of ^{31}P chemical shifts was able to distinguish between **6** and **7** as the structure of a



6



7

particular reaction product.[37] Although ^{12}C has no spin, ^{13}C has a spin number of $\frac{1}{2}$, and some instruments are sensitive enough to pick up ^{13}C signals, even at the natural abundance of 1.1%. Much information can be learned from these spectra, since C—C spin-spin coupling is practically nonexistent, owing to the low probability that one ^{13}C will be adjacent to another. However, ^{13}C does couple with protons.

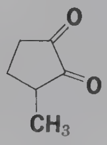
---

[35] For discussions of the variation of chemical shift with structure, see Jackman, Ref. 24, pp. 50–81, and Conroy, Ref. 24, pp. 273–291. Tables of chemical shifts are given by Chamberlain, *Anal. Chem.* **31**, 56–77 (1959), and Mohacsi, *J. Chem. Educ.* **41**, 38 (1964). Also see Ref. 2, pp. 136–144.

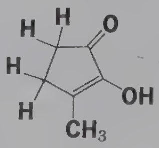
[36] Jackman, Ref. 24, pp. 52–57.

[37] Jones, Katritzky, and Michalski, *Proc. Chem. Soc.* **1959**, 321.

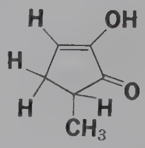
A number of examples will be given of structural problems solved with proton magnetic resonance. Evidence indicated that **8** existed as a monoenol,



8



9



10

but the question to be solved was, which enol, **9** or **10**? The spectrum is reproduced in Figure 9.[38] From the chemical shift, the peak at 3.25 τ is an OH peak, the one at 7.57 is a CH_2, and the one at 7.97 a CH_3 peak. The area ratios are 1:4:3. This is in accord with structure **9**, but not with **10**, which would display five peaks in a ratio 1:1:1:2:3. In addition, the CH_3 peak was unsplit, indicating no hydrogens on the adjacent carbon. It might be expected that the two CH_2 groups, being nonequivalent, would absorb at different places, but both are α to a double bond and apparently are similar enough to absorb together. For the same reason they do not split each other.

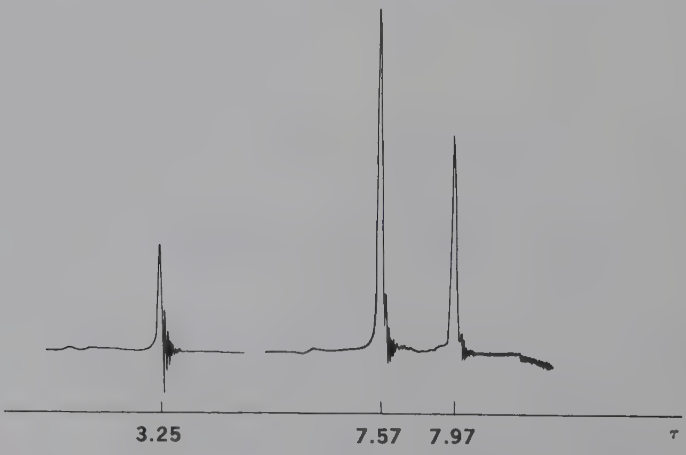
Another example[39] shows how area ratio often proves decisive. The oxidation of cyclooctatetraene gave a compound which might be **11**, **12**, or **13**. The spectrum showed only two peaks, with an area ratio of 3:1, compatible only with **11**. An example which shows how infrared evidence may be used

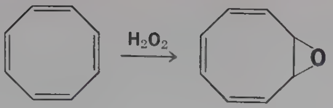
---

[38] Bredenberg, *Acta Chem. Scand.* **13**, 1733 (1959).

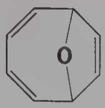
[39] Cope, Moore, and Moore, *J. Am. Chem. Soc.* **80**, 5505 (1958).

Figure 9. *Nmr spectrum of 3-methyl-1,2-cyclopentanedione.*[38]

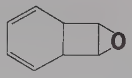




11

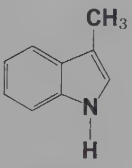


12

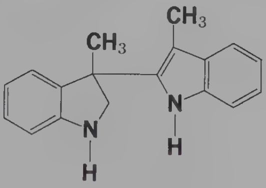


13

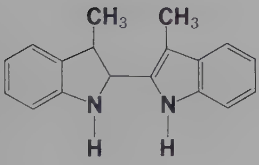
in conjunction with nmr is the following. Skatole (**14**) forms a dimer, which might be **15**, **16**, or **17**.[40] The infrared spectrum showed two NH groups and ruled out **17**. The nmr spectrum showed, among other peaks, two peaks in the CH_3 region, a doublet and a singlet, each of area corresponding to three protons. If **15** were the structure, neither methyl peak would be split, but in **16** one methyl is split by the adjacent CH group. The structure is thus **16**.



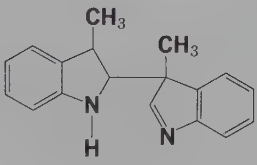
14



15



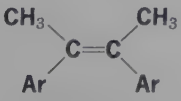
16



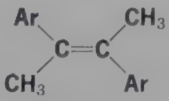
17

Finally, the unexpected spectrum of allylmagnesium bromide may be mentioned. This spectrum showed only two peaks, with an area ratio of 4:1; the CH peak split into five parts, and the CH_2 peak split into two.[41] The only possibility in accord with this is rapid (faster than 10^3 sec^{-1}) exchange between $MgCH_2CH{=}CH_2$ and $CH_2{=}CHCH_2Mg$.

2. *Determination of configuration.* There are several ways in which nmr may be used to determine configuration. A proton on a double-bond carbon has a different chemical shift if it is cis to a particular group than if it is trans. This also applies to protons on a methyl group. Thus, for a series of 1,2-dimethylstilbenes, the methyl groups of the cis isomers (**18**) were found at a lower field than the trans compounds (**19**).[42] In addition, a methyl group



18



19

---

[40] Hinman and Shull, *J. Org. Chem.* **26**, 2339 (1961).

[41] Nordlander and Roberts, *J. Am. Chem. Soc.* **81**, 1769 (1959).

[42] Inamoto, Masuda, Nagai, and Simamura, *J. Chem. Soc.* **1963**, 1433.

on a double bond is split into two parts by a hydrogen attached to the other side of the double bond, and the coupling constant is usually, though not always, greater from a hydrogen that is cis to the methyl group.[43]

3. *Determination of conformation.* If a molecule can exist in several conformations which rapidly interconvert, then any proton in the molecule assumes all possible positions in a very short time, and the nmr spectrum represents an average. This is the case in most open-chain compounds. Even in cyclohexanes the chair-chair interconversion is so rapid that the nmr spectrum shows only one peak. However, in cases where interconversion of conformers is slowed or prevented, either by cooling the compound or by the inherent structure of the molecule, then the hydrogens of each conformer appear separately (or in cases where only one is stable, then only that one appears). An example is the cooling of cyclohexane to $-110°$, at which temperature two peaks appear. Only the chair form is present, and one peak is due to the equatorial and the other to the axial hydrogens.[44]

When axial and equatorial protons do appear at different positions, they can often be told apart, since axial protons usually absorb at a slightly higher field than equatorials.[45] However, care must be taken, since this is not always the case.[46] In some cases, better values may be obtained from other nuclei, if they lend themselves to nmr. For example, axial and equatorial protons differ in chemical shift by a small amount, but the difference between axial and equatorial ^{19}F is an order of magnitude greater.[47] Another aid to conformation determination is the fact that the coupling constant J is higher for coupling between two adjacent axial hydrogens than for two equatorials or for an axial and an equatorial.[48]

Energy barriers for shifts between cyclohexane conformers have been calculated from the shape of the peak and the way it splits with decreasing temperature.[49]

Of course, determination of conformation very often determines the configuration as well.

4. *Determination of equilibrium constants in tautomeric systems.* When tautomers interconvert at a rate slower than about 10^3 sec^{-1}, the nmr spectrum shows separate peaks for each tautomer. Comparison of peak areas gives the proportions of each, and the equilibrium constant may be determined.[50] It is not always easy in these cases to tell which peak comes from

[43] Jackman and Wiley, *J. Chem. Soc.* **1960**, 2881.

[44] For reviews of the use of nmr to study conformational mobility in cyclic systems, see Anderson, *Quart. Rev. (London)* **19**, 426–439 (1965); and Franklin and Feltkamp, *Angew. Chem. Intern. Ed. Engl.* **4**, 774–783 (1965).

[45] Eliel, *Chem. Ind. (London)* **1959**, 568; Lemieux, Kullnig, Bernstein, and Schneider, *J. Am. Chem. Soc.* **80**, 6098 (1958).

[46] Williamson and Johnson, *J. Am. Chem. Soc.* **83**, 4623 (1961); Wellman and Bordwell, *Tetrahedron Letters* **1963**, 1703; Nickon, Castle, Harada, Berkoff, and Williams, *J. Am. Chem. Soc.* **85**, 2185 (1963).

[47] Bovey, Anderson, Hood, and Kornegay, *J. Chem. Phys.* **40**, 3099 (1964).

[48] Trager, Vincenzi, and Huitric, *J. Org. Chem.* **27**, 3006 (1962).

[49] For example, see Jensen, Noyce, Sederholm, and Berlin, *J. Am. Chem. Soc.* **84**, 386 (1962); Harris and Sheppard, *Proc. Chem. Soc.* **1961**, 418; and Kaplan and Meloy, *Tetrahedron Letters* **1964**, 2427.

[50] For example, see Burdett and Rogers, *J. Am. Chem. Soc.* **86**, 2105 (1964).

which compound, but in some cases spin-spin coupling occurs in one and not the other.[51] Certain other equilibrium mixtures may also be analyzed in this way.

5. *Measurement of electronegativity.* Since in the absence of a magnetically anisotropic group (p. 184), the chemical shift is approximately proportional to the electron density around the proton, determination of chemical shifts becomes a method of determining electronegativity. The greater the electronegativity of the group attached to the proton, the lower the electron density around the proton. Since inductive effects are based on electronegativity, they may be studied by this method. An example of the use of this correlation is found in the variation of chemical shift of the *ring* protons in the series toluene, ethylbenzene, isopropylbenzene, *tert*-butylbenzene (there is a magnetically anisotropic group here, but its effect should be constant throughout the series). It is found that the electron density surrounding the ring protons decreases in the order given.[52] This is an example of the Baker-Nathan effect, in which *tert*-butyl is less electron-donating than methyl (p. 57). However, this type of correlation is by no means perfect, since all of the measurements are being made in a powerful field, which itself may affect the electron-density distribution. Coupling constants between the two protons of a system $-\underset{|}{\mathrm{C}}\mathrm{H}-\underset{|}{\mathrm{C}}\mathrm{H}-\mathrm{X}$ have also been found to depend on the electronegativity of X.[53]

6. *Further electron-density information.* For carbons involved in π bonding, ^{13}C chemical shifts correlate with the π-electron density on the carbon.[54] For example, ^{13}C nmr spectra for a series of carbonyl compounds ($R^{13}COR'$) in a variety of solvents showed that the ^{13}C chemical shift was approximately proportional to the polarity of the $C{=}O$ bond.[55] It has also been found that ^{14}N chemical shifts of nonaromatic nitro compounds are dependent on the electronegativity of the rest of the molecule.[56]

The coupling constant between ^{13}C and a hydrogen directly attached to it has been reported to be a linear function of the amount of s character of the orbitals of that carbon atom.[57] However, this relationship is not completely general, because other factors, such as the geometry of the molecule and electronegativity effects, also affect the coupling constants.[58]

7. *Aromaticity.* As mentioned on page 185, protons on a ring are greatly deshielded (appear at low τ) if the ring contains a closed loop of electrons. This is the first direct criterion for establishment of aromaticity. In large

---

[51] Dudek, *J. Am. Chem. Soc.* **85,** 694 (1963).

[52] Moodie, Connor, and Stewart, *Can. J. Chem.* **38,** 626 (1960).

[53] Williamson, *J. Am. Chem. Soc.* **85,** 516 (1963); Laszlo and Schleyer, *J. Am. Chem. Soc.* **85,** 2709 (1963).

[54] Karplus and Pople, *J. Chem. Phys.* **38,** 2803 (1963).

[55] Maciel, *J. Chem. Phys.* **42,** 2746 (1965); Maciel and Natterstad, *J. Chem. Phys.* **42,** 2752 (1965).

[56] Witanowski, Urbánski, and Stefaniak, *J. Am. Chem. Soc.* **86,** 2569 (1964).

[57] See, for example, Muller and Pritchard, *J. Chem. Phys.* **31,** 768, 1471 (1959); Juan and Gutowsky, *J. Chem. Phys.* **37,** 2198 (1962); Foote, *Tetrahedron Letters* **1963,** 579; Olah and Comisarow, *J. Am. Chem. Soc.* **88,** 1818 (1966); and Douglas, *J. Chem. Phys.* **45,** 3465 (1966).

[58] Muller and Rose, *J. Am. Chem. Soc.* **84,** 3975 (1962); Karabatsos and Orzech, *J. Am. Chem. Soc.* **87,** 560 (1965); Brown and Puckett, *J. Chem. Phys.* **44,** 2238 (1966).

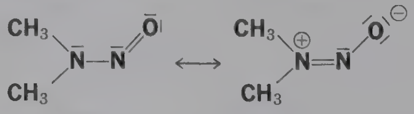
rings, protons may be directed *inside* the ring, and thus should be greatly shielded (appear at high τ) if an aromatic loop is present. In [18]annulene (**61** in Chapter 2, p. 52) there are 12 protons outside the ring and 6 inside. The nmr spectrum shows two peaks: one, due to 6 protons, is at $\tau = 11.8$, and the other, due to 12 protons, is at $\tau = 1.1$. The expectation has been fulfilled: the inner protons are found at an even higher position than the normal alkyl-proton region, and much higher than the olefinic region, and the other protons at very low τ, as expected for aromatic protons.[59] It is an interesting phenomenon that for [16]- and [24]annulene, which do not obey Hückel's rule (see p. 53), this behavior is reversed; that is, inner protons appear at low field, and outer protons at high field.[59a] It must be emphasized once again that the ring-current criterion for aromaticity is not directly related to the criteria based on resonance energy and reactivity (see pp. 52–53).[60]

8. *Detection of hydrogen bonding.* Hydrogen bonding involves rapid exchange, and thus the nmr spectrum records an average value. Hydrogen bonding *can* be detected, though, because it usually produces a shift to lower field. The small degree of hydrogen bonding in ethyl mercaptan was detected in this manner.[61] Hydrogen bonding changes with temperature and concentration, and comparison of spectra taken under different conditions also serves to detect and measure it. As with infrared spectra, intramolecular hydrogen bonding may be distinguished from intermolecular by its constancy when the concentration is varied.

9. *Acid-base constants.* Acid-base reactions also involve very fast proton transfers. However, the average chemical shift can be plotted against concentration to give the degree of dissociation.

10. *Quantitative analysis.* As with infrared and ultraviolet peaks, the nmr peaks of a compound present in a solvent have heights proportional to the concentration. Thus the nmr spectrum can also be used for quantitative analysis, although up to now it has not been used much for this purpose.

11. *Special problems.* Occasionally a problem arises, not in any of the above categories, which can be nicely solved by nmr. An example is the determination of resonance in **20**. Does **21** contribute to the hybrid? It may be observed that **20**, in the absence of a contribution from **21**, would display rapid rotation (faster than 10^3 sec^{-1}) about the N—N bond, and the nmr spectrum would show only one methyl peak; but in **21** free rotation is slowed to less than 10^3 sec^{-1} or prevented altogether, and two methyl peaks would be expected. At 25° two peaks are obtained, but at 193°, there is just one.[62]



20 **21**

---

[59] Jackman, Sondheimer, Amiel, Ben-Efraim, Gaoni, Wolovsky, and Bothner-By, *J. Am. Chem. Soc.* **84,** 4307 (1962).

[59a] Calder and Sondheimer, *Chem. Commun.* **1966,** 904.

[60] Abraham and Thomas, *J. Chem. Soc.* **1966(B),** 127.

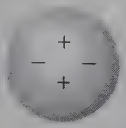
[61] Forsén, *Acta Chem. Scand.* **13,** 1472 (1959).

[62] Looney, Phillips, and Reilly, *J. Am. Chem. Soc.* **79,** 6136 (1957).

Nmr is a method which complements infrared and electronic spectra and does not supplant them. In many problems, two or all three methods are jointly used, usually with good results.

Other Magnetic Methods. There are two other magnetic methods from which structural information may be obtained.

1. *Nuclear quadrupole resonance.*[63] This method is restricted to nuclei with spin numbers greater than $\frac{1}{2}$. Such nuclei are quadrupoles; there is an uneven charge distribution inside the nucleus:



Nuclear quadrupole resonance is in some respects similar to nmr, but instead of an external magnetic field, the field used is the one caused by the electrons of the molecule (only inhomogeneous electrons—those not in inner shells or *s* orbitals—can give rise to the field). Since the strength of this field cannot be changed, the applied frequency must be varied (the range is 10^6 to 10^9 cycles/sec).

From the spectrum so obtained can be calculated *quadrupole coupling constants* (eQq),[64] which express the inhomogeneity of the electron field close to the nucleus. Three types of information may be obtained from these constants. The first of these is the percentage of ionic character in a covalent bond. For example, eQq for $K^{35}Cl$ gas is -0.041 Mc/sec, but for $CH_3{}^{35}Cl$ gas is -74.8 Mc/sec. This is so because a chloride ion has a homogeneous electron distribution and thus no quadrupole moment at all, while covalent bonding distorts the outer electrons.[65] Of course, electronegativity values can be calculated from these types of data. In contrast to dipole-moment measurements, this method can show the electron distribution of a single bond in a larger molecule. Thus, it has been determined that the ionic character of any one C—Cl bond decreases in the series from CH_3Cl to CCl_4. A second type of information concerns hybridization. Since *s* electrons are spherically symmetrical, but *p* electrons are not, the state of hybridization can often be calculated. For example, in FCl the bond contains 18% *s* character with respect to the chlorine.[66] Unfortunately, in most molecules, only one number (eQq) is available (in some cases, such as $^{35}Cl—^{79}Br$, we can get two, one for each nucleus), and it is not always possible to tell how much of the electron inhomogeneity is caused by partial ionic character and how much by hybridization. Information to help decide must come from other sources. A third type of information, the percentage of double-bond character, may be obtained in certain cases.[67]

---

[63] For reviews, see O'Konski, in Nachod and Phillips, "Determination of Organic Structures by Physical Methods," vol. 2, pp. 661–726, Academic Press Inc., New York, 1962; and Orville-Thomas, *Quart. Rev.* (*London*) **11**, 162–188 (1957).

[64] e is the charge on the proton, Q is the nuclear quadrupole moment, and q is the field gradient.

[65] In the case of ^{35}Cl, a higher negative value indicates a less homogeneous electron density.

[66] Gordy, *J. Chem. Phys.* **19**, 792 (1951).

2. *Electron paramagnetic resonance* (*epr*).[68] This method, also called *electron-spin resonance,* is also similar to nmr, but it is not *nuclear* spin that is affected, but the spin of the electron. Since two electrons in an orbital always have opposite spins which cancel, only molecules with unpaired electrons have an epr spectrum. In organic chemistry this means that the method is limited to free radicals and triplet species. An external field is applied, and the radio frequency necessary to cause the electron to flip is about 10 to 20 Mc/sec, depending on the field strength. Since few organic free radicals are stable at room temperature, measurements are frequently made at low temperatures (77°K is often used, since this is the temperature of a liquid-nitrogen bath) or on free radicals trapped in lattices.

Epr has had three principal uses in organic chemistry. The area under the curve is proportional to the actual number of unpaired electrons in the sample cell; hence the concentration of free radicals may be determined. The change in concentration with time may be used as a way of measuring the rates of reactions involving free radicals.[69] But the chief use is to study the distribution within the molecule of the orbital containing the unpaired electron. This can be determined by an examination of the splitting pattern. The peak is split by neighboring protons in a manner similar to the splitting of nmr peaks. For example, the methyl radical shows a 1:3:3:1 pattern, indicating a splitting by three protons, and showing that the orbital containing the unpaired electron is symmetrically distributed.[70] In addition, epr has been used to study rotational barriers in free radicals.[71]

Mass Spectra. Mass spectrometry is a technique which has been in use since about 1910, but only in recent years has it been applied extensively to organic molecules.[72] In this method a very small sample (0.1 to 1 mg) is vaporized and bombarded with low-energy electrons. This produces positive ions, which are formed from the original molecule either by direct loss of one or more electrons or by bond cleavage so that the molecule is fragmented into two or more pieces. By means of electric and magnetic fields, the positive ions are caused to travel in such a way that they are segregated according to mass-to-charge ratio (m/e). There are thus a number of beams, each containing ions with only one m/e, and each beam is deflected by the fields so that it strikes a photographic plate at a certain position. The intensity of each peak is recorded on the spectrum, so that we know how much of each ion of a given m/e was formed by the original bombardment. Electrical recording is also used. This separation is so sensitive that it can easily separate isotopes, and this was the earliest use of the method. It is now possible to use mass spectrometry for ions of molecular weight up to 1000, and even higher, and nonvolatile compounds may also be used.[73]

---

[67] See O'Konski, Ref. 63, pp. 701–706.

[68] This method is treated in the Weissberger series (see Ref. 5), by Fraenkel, vol. 1, part 4, pp. 2801–2872, and in "Determination of Organic Structures by Physical Methods" (see Ref. 5) by Bersohn, vol. 2, pp. 563–616. For a monograph, see Bersohn and Baird, "An Introduction to Electron Paramagnetic Resonance," W. A. Benjamin, Inc., New York, 1966. For other review articles, see Carrington, *Quart. Rev.* (*London*) **17**, 67–99 (1963); Symons, *Advan. Phys. Org. Chem.* **1**, 284–363 (1963); and Schneider, Möbius, and Plato, *Angew. Chem. Intern. Ed. Engl.* **4**, 856–867 (1965).

[69] For a review, see Sommer, *Bull. Soc. chim. France* **1964**, 2373–2380.

[70] Bersohn, Ref. 68, p. 579.

[71] Stone and Maki, *J. Chem. Phys.* **37**, 1326 (1962).

[72] For books on mass spectrometry in organic chemistry, see Biemann, "Mass Spectrometry: Organic Chemistry Applications," McGraw-Hill Book Company, New York, 1962; Beynon, "Mass Spectrometry and Its Applications to Organic Chemistry," Elsevier Publishing Company, Amsterdam, 1960; McLafferty, "Mass Spectrometry of Organic Ions, Academic Press Inc., New York, 1963; and Budzikiewicz, Djerassi, and Williams, "Interpretation of Mass Spectra in Organic Compounds," Holden-Day, San Francisco, 1964. This subject is treated in the Weissberger series (see Ref. 5) by Stewart, vol. 1, part 4, pp. 3449–3539, and Biemann, vol. XI, part 1, pp. 261–316; and in "Determination of Organic Structures by Physical Methods" (see Ref. 5), by McLafferty, vol. 2, pp. 93–179. For review articles, see Biemann, *Angew. Chem. Intern. Ed. Engl.* **1**, 98–111 (1962); Reed, *Advan. Org. Chem.* **3**, 1–73 (1963); and Spiteller and Spiteller-Friedman, *Angew. Chem. Intern. Ed. Engl.* **4**, 383–393 (1965). See also Budzikiewicz, Djerassi, and Williams, "Structural Elucidation of Natural Products by Mass Spectroscopy," 2 vols., Holden-Day, San Francisco, 1964.

The chief use of mass spectrometry in organic chemistry is for structure determination, and this is done in various ways. For most compounds, the principal peak is the one in which the original molecule has lost only one electron, and the mass corresponding to this peak is the molecular weight of the molecule. Consequently, mass spectrometry is one of the few general methods of molecular-weight determination which is accurate to the individual mass unit. Much information can also be obtained from the other peaks, since the mass of each peak corresponds to a particular fragment torn from the molecule, and molecules are usually broken in certain places more readily than in others. For example, in an alkylbenzene an important position of cleavage is between C-1 and C-2 of the side chain so that the benzyl cation (which rearranges to the tropylium ion, see p. 43) remains, while primary alcohols show a great tendency to cleave so that $^+CH_2OH$ is a fragment. In inspecting a mass spectrum of an unknown compound, one may attempt to discover to which ion each peak corresponds by examining a table of ions arranged in order of m/e.[74] However, such a procedure is usually not helpful unless one already has a good idea which groups are likely to be present. The reason is that there are many possible ions which can correspond to each m/e. For example, Reference 74 lists eight empirical formulas for ions whose m/e is 59. If other information is available, then the possibilities may be sharply reduced. Of course, even when the structure of a particular ion is determined, it is not always certain that this is a moiety actually present in the molecule. Rearrangement of carbonium ions is common, and, for example, a peak for $CH_3CH_2^+$ is obtained upon mass spectrometry of isobutane. In this case rearrangement occurred before fragmentation.

Recently, the technique of *high-resolution mass spectrometry*[75] has been developed, in which ions of slightly different m/e ratios may be resolved. By this means, the eight empirical formulas for $m/e = 59$ would all appear at different points, since, for example, m/e for CHNS is 58.9829; for $C_2H_3O_2$ is 59.0133; and for C_3H_7O is 59.0496. By this technique, which is sensitive to as little as 1/28,000 of the total mass, the m/e for a peak in most cases could apply to ions of only one empirical formula, greatly facilitating structural interpretation. Isomeric ions, of course, could not be distinguished; hence C_3H_7O, for example, could apply to $(CH_3)_2C^+OH$, $CH_3CH_2OCH_2^+$, etc. Application of the high-resolution technique to the principal peak gives in most cases not only the molecular weight of the original compound, but also its molecular formula. Interpretation of complex high-resolution mass spectra may be aided by computer analysis.[76] The computer prints a list of formulas for molecular fragments.

---

[73] Lynch, Wilson, Budzikiewicz, and Djerassi, *Experientia* **19**, 211 (1963).

[74] Such a table is in McLafferty, "Mass Spectral Correlations," *Advan. Chem. Ser.* **40** (1963).

[75] For a review, see Biemann, *Pure Appl. Chem.* **9**, 95–118 (1964).

Since even ordinary mass spectrometry is sensitive enough to separate isotopes, then a methyl ion, say, will appear at more than one place. There will be a peak at *m/e* 15 for $^{12}C^1H_3$, but also a much smaller peak at 16 for $^{13}C^1H_3$ and $^{12}C^2H^1H_2$, and an even smaller peak at 17. From the known natural abundances of the various isotopes and the ratio of peak heights, the percentage composition, and consequently the empirical formula, may often be calculated, not only for the principal peak but also for the others. For example, a peak at *m/e* 132, which is due to C_9H_8O, has a 133:134 ratio of 9.9:0.69, while a similar peak due to $C_8H_8N_2$ has a 133:134 ratio of 9.52:0.39.

Mass spectrometry has other uses for the organic chemist. The total spectrum is as much a fingerprint as an infrared spectrum, and exact overlap (within 1% on peak heights) of two spectra indicates identity of two samples, although here too enantiomers give the same spectrum.[77] However, care must be taken, since in certain cases (as with the three xylenes) positional isomers give spectra which are very similar. In many cases, interpretation of mass spectra can detect mixtures, since fragments may be present which are not compatible with a single structure. In these cases and in known mixtures, it is often possible to use mass spectra for qualitative analysis, since structures can be determined for more than one component from one mass spectrum. If the components of a mixture are known, then quantitative analysis is possible by measurements of peak intensities. Detection of the presence of nonradioactive isotopes, such as deuterium or ^{13}C, is an important use of mass spectroscopy. Another use is determination of bond strengths. If the energy of the ionizing radiation is increased until it is just strong enough to cause ionization, the voltage at which ionization begins is called the *appearance potential.* From this the bond strength may be calculated.

Other Instrumental Methods. Electron-diffraction, x-ray-diffraction, and dipole-moment measurements are highly useful for determination of organic structures, but these methods are beyond the scope of this book, since they are seldom used directly by organic chemists.[78]

---

[76] Biemann and McMurray, *Tetrahedron Letters* **1965**, 647.

[77] This is true only if the spectra are measured on the same or a similar instrument, under more or less the same conditions. Otherwise two spectra of the same compound generally give the same peaks, but their heights may greatly differ.

[78] For x-ray diffraction, see, in the Weissberger series (Ref. 5), Lipscomb, vol. 1, part 2, pp. 1641–1738; and in "Determination of Organic Structures by Physical Methods" (Ref. 5), Robertson, vol. 1, pp. 463–502. For electron diffraction, see, in the Weissberger series, Brockway, vol. 1, part 2, pp. 1739–1762; and in "Determination of Organic Structures by Physical Methods," Karle and Karle, vol. 1, pp. 427–461. For dipole-moment measurements, see, in the Weissberger series, Smyth, vol. 1, part 3, pp. 2599–2634; and in "Determination of Organic Structures by Physical Methods," Sutton, vol. 1, pp. 373–425.

CHAPTER SEVEN

Mechanisms and Methods of Determining Them

A mechanism is the actual process by means of which a reaction takes place —which bonds are broken, in what order, how many steps are involved, the relative rate of each step, etc. In order to state a mechanism completely, we should have to specify the positions of all atoms, including those in solvent molecules, and the energy of the system, at every point in the process. A proposed mechanism must fit all the facts available. It is always subject to change as new facts are discovered. The usual course of a discovery is that the gross features of a mechanism are the first to be known, and that increasing attention is paid to finer details. The tendency is always to probe more deeply, to get more detailed descriptions.

Although for most reactions gross mechanisms may today be written with a good degree of assurance, no mechanism is known completely. There is much about the fine details which is still puzzling, and for some reactions even the gross mechanism is still not clear. Many facts are not yet understood. The problems involved are very difficult because there are so many variables. Many examples are known where reactions proceed by different mechanisms under different conditions. In many cases there are several proposed mechanisms each of which completely explains all the data.

Types of Mechanism. In any reaction bonds are broken and/or bonds are formed. When a covalent bond is broken so that the molecule is cleaved into two parts, the two electrons in the orbital may remain with one of the fragments, or they may split up, so that each fragment carries one electron. This basic difference in the process of bond breaking allows us to classify all mechanisms into two basic types: *polar* and *free-radical.* Reactions in which the electrons move only in pairs are polar reactions, while those which involve unpaired electrons are free-radical reactions. These reaction types are also called *heterolytic* and *homolytic,* respectively, especially by British chemists.

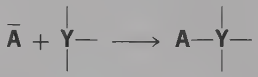
Polar reactions may be grossly classified into seven types. These types are descriptions of net changes; the actual process may involve several steps. Polar reactions do not necessarily involve ionic intermediates. The important thing is that the electrons are never unpaired. For some reaction types it is convenient to call one reactant the *attacking reagent* and the other the *substrate.* We shall always designate as the substrate that molecule which is organic. When both reactants are organic, then the one supplying the carbon to the new bond is the substrate. When carbon-carbon bonds are formed, it is necessary to be arbitrary about which is the substrate and which the attacking reagent.

If a reagent brings a pair of electrons to the substrate, it is called a *nucleo-*

phile, and the reaction is called *nucleophilic.* If the reagent takes a pair of electrons from the substrate, it is an *electrophile,* and the reaction is *electrophilic.* In a reaction in which the substrate molecule becomes cleaved, then part of it (the part not containing the carbon) is usually called the *leaving group.*

In the description of the seven types, which follows, the immediate products are shown, though in many cases they then combine with something else. All of the species are shown without charges, since differently charged reactants may undergo analogous changes. The descriptions of the seven types given here are purely formal and are for the purpose of classification and comparison. All but the first two are discussed in detail in Part 2 of this book.

1. Reactions in which one reactant contributes an unshared pair of electrons to another which has an empty orbital available



$$\bar{\text{A}} + \overset{|}{\underset{|}{\text{Y}}}\text{—} \longrightarrow \text{A—}\overset{|}{\underset{|}{\text{Y}}}\text{—}$$

This is simply a Lewis acid-base reaction.

2. *Simple cleavage.*

$$\text{A—X} \longrightarrow \bar{\text{A}} + \text{X}$$

This is the reverse of the first type. Not many organic reactions may be simply classified in the first two categories.

3. *Substitution.* These are classified as nucleophilic or electrophilic, depending on which reactant is designated as the substrate and which as the attacking reagent (very often Y must first be formed by a previous bond cleavage).

Nucleophilic substitution (Chapters 10, 13)

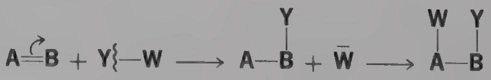
$$\text{A}\}\text{—X} + \bar{\text{Y}} \longrightarrow \text{A—Y} + \bar{\text{X}}$$

Electrophilic substitution (Chapters 11, 12)

$$\text{A—}\{\text{X} + \text{Y} \longrightarrow \text{A—Y} + \text{X}$$

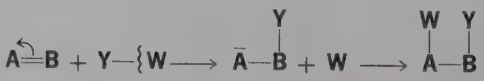
4. *Addition to double or triple bonds* (Chapters 15, 16). The initial attack may be nucleophilic or electrophilic, or both sides may be simultaneously attacked.

Electrophilic addition



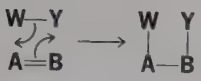
$$\text{A}\overset{\curvearrowright}{=}\text{B} + \text{Y}\}\text{—W} \longrightarrow \text{A—}\overset{\text{Y}}{\overset{|}{\text{B}}} + \bar{\text{W}} \longrightarrow \overset{\text{W}}{\overset{|}{\text{A}}}\text{—}\overset{\text{Y}}{\overset{|}{\text{B}}}$$

Nucleophilic addition



$$\text{A}\overset{\curvearrowleft}{=}\text{B} + \text{Y—}\{\text{W} \longrightarrow \bar{\text{A}}\text{—}\overset{\text{Y}}{\overset{|}{\text{B}}} + \text{W} \longrightarrow \overset{\text{W}}{\overset{|}{\text{A}}}\text{—}\overset{\text{Y}}{\overset{|}{\text{B}}}$$

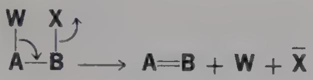
Simultaneous addition



$$\overset{W-Y}{A{=}B} \longrightarrow \overset{W}{A}-\overset{Y}{B}$$

The examples show Y and W as coming from the same molecule, but very often they come from different molecules. Also, the examples show the Y—W bond cleaving at the same time that Y is bonding to B, but often this cleavage takes place earlier.

5. *Elimination* (Chapter 17).

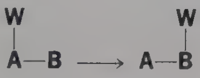


$$\overset{W}{A}-\overset{X}{B} \longrightarrow A{=}B + W + \bar{X}$$

W and X may or may not leave simultaneously, and they may or may not combine.

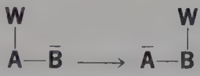
6. *Rearrangement* (Chapter 18). The migrating group nearly always carries the electron pair with it.

Shift with electrons



$$\overset{W}{A}-B \longrightarrow A-\overset{W}{B}$$

Shift without electrons (rare)



$$\overset{W}{A}-\bar{B} \longrightarrow \bar{A}-\overset{W}{B}$$

The illustrations show 1,2-rearrangements, in which the migrating group moves to the adjacent atom. These are the most common, although longer rearrangements are also possible. There are also some rearrangements which do not involve simple migration at all (see Chapter 18).

7. Reactions which are combinations of two or more of the above types. In this book such reactions will be treated under whichever classification seems most important.

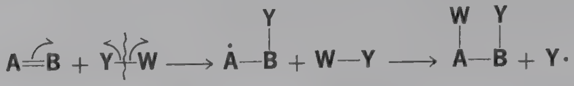
Free-radical reactions may be formally classified in a similar way, although there are no net reactions similar to the first two types, and very few eliminations proceed by free-radical mechanisms, except at high temperatures (also see pp. 156 and 521).

1. *Substitution* (Chapter 14).

$$A-X + Y\cdot \longrightarrow A-Y + X\cdot$$

Since few free radicals are stable, Y· is usually produced *in situ* by a free-radical cleavage reaction, and X· goes on to react further.

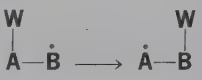
2. *Addition to double and triple bonds* (Chapter 15).



$$A{=}B + Y{-}W \longrightarrow \dot{A}{-}\overset{Y}{B} + W{-}Y \longrightarrow \overset{W}{A}{-}\overset{Y}{B} + Y\cdot$$

As with ionic addition, Y and W may and often do come from different molecules.

3. *Rearrangements* (Chapter 18).



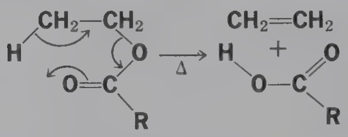
$$\overset{W}{A}{-}\dot{B} \longrightarrow \dot{A}{-}\overset{W}{B}$$

This is not a net reaction either, since the starting radical must be produced, and the product must usually react further.

4. *Combinations of these.*

Note that in this book we use single-headed arrows to indicate the movement of unpaired electrons.

There are a number of reactions which proceed by cyclic mechanisms, usually involving a six-membered, but in some cases a four-membered, transition state. An example is the pyrolysis of esters (reaction **7-3**, p. 756).



These reactions have been called *four-center* or *six-center* reactions. There are no intermediates, ionic or free-radical. Some of the reactions are formally eliminations (as in the above example), some are rearrangements (e.g., the Claisen rearrangement, reaction **8-25**, p. 830), and some are additions (e.g., the Diels-Alder reaction, **5-34**, p. 626). In this book, they are not considered together, but each under its formal category.

Thermodynamic and Kinetic Requirements for Reaction. The thermodynamic requirement for a reaction to occur spontaneously is that the free energy of the products be lower than the free energy of the reactants, that is, that ΔG be negative. Reactions may go the other way, of course, but only if free energy is added. However, for most reactions, whether ΔG is negative or not, there is also a kinetic requirement. Free energy of activation ($\Delta G^{\ddagger}$) must be added for a reaction to occur. This situation is illustrated in Figure 1,[1] which is an energy profile[2] for a one-step reaction without an intermediate. In this type of diagram the horizontal axis signifies the progression of the reaction.

---

[1] Strictly speaking, this is an energy profile for a reaction of the type $XY + Z \rightarrow X + YZ$. However, it may be applied, in a rough way, to other reactions.

[2] For a fuller discussion, see Frost and Pearson, "Kinetics and Mechanism," 2d ed., pp. 77–102, John Wiley & Sons, Inc., New York, 1961.

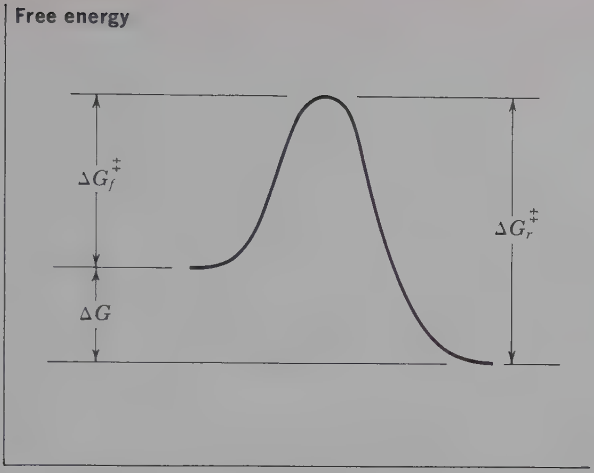


Figure 1. *Energy profile of a reaction without an intermediate where the products have a lower free energy than the reactants.*

$\Delta G_f^\ddagger$ is the free energy of activation for the forward reaction. If the reaction shown in Figure 1 is reversible, then $\Delta G_r^\ddagger$ must be greater than $\Delta G_f^\ddagger$, since it is the sum of ΔG and $\Delta G_f^\ddagger$.

When a reaction between two or more molecules has progressed to the point corresponding to the top of the curve, the term *transition state* is applied to the positions of the nuclei and electrons. The transition state possesses a definite geometry and charge distribution. The system at this point is called an *activated complex.*

In the *transition-state theory* the starting materials and the activated complex are taken to be in equilibrium, the equilibrium constant being designated $K^\ddagger$. According to the theory, all activated complexes go on to product at the same rate, so that the rate constant (see p. 208) of the reaction is dependent only on the position of the equilibrium between the starting materials and the activated complex, that is, on the value of $K^\ddagger$. $\Delta G^\ddagger$ is related to $K^\ddagger$ by

$$\Delta G^\ddagger = -2.3RT \log K^\ddagger$$

so that a higher value of $\Delta G^\ddagger$ indicates a smaller rate constant. Some reactions have no free energy of activation at all, meaning that $K^\ddagger$ is essentially infinite and that virtually all collisions lead to reaction. Such processes are said to be *diffusion-controlled.*

Reactions with intermediates are two-step (or more) processes. In these reactions there is an energy "well." There are two transition states, each with an energy higher than the intermediate (Figure 2). The deeper the well, the more stable the intermediate. In Figure 2 the second peak is higher than the first, but the opposite situation is also possible.

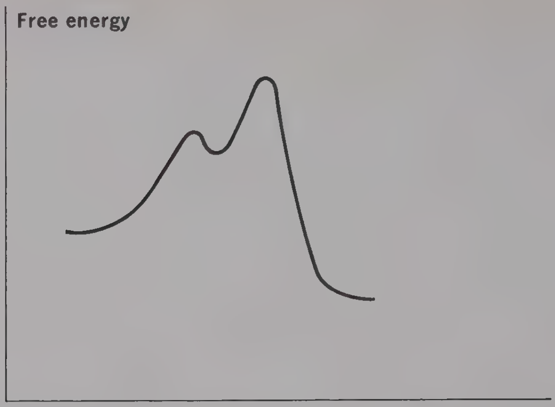
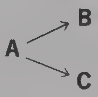


Figure 2. *Free-energy profile for a reaction with an intermediate.*

There are many cases in which a compound under a given set of reaction conditions may undergo competing reactions to give different products.



If neither reaction is reversible, then the product formed in larger amount will be the one which is formed faster, regardless of its thermodynamic stability. The product is said to be *kinetically controlled.* However, if the reactions are reversible, then this will not necessarily be the case. If such a process is stopped well before the equilibrium has been established, the reaction will be kinetically controlled since more of the faster-formed product will be present. However, if the reaction is permitted to approach equilibrium, then the predominant product will be the thermodynamically more stable one, i.e., the one with the lower free energy. Here we say the product is *thermodynamically controlled.* Of course, it is possible for the product formed faster to be also more stable thermodynamically.

Microscopic Reversibility. In the course of a reaction the nuclei and electrons assume positions which at each point correspond to the lowest free energies possible. If the reaction is reversible, then these positions must be the same in the reverse process, too. This means that the forward and reverse reactions (run under the same conditions) must proceed by the same mechanism. This is called the *principle of microscopic reversibility.* For example, if in a reaction A $\longrightarrow$ B there is an intermediate C, then C must also be an intermediate in the reaction B $\longrightarrow$ A. This is a useful principle since it enables us to know the mechanism of reactions in which the equilibrium lies far over to one side. Reversible photochemical reactions are an exception, since a molecule which has been excited photochemically does not have to lose its energy in the same way.

METHODS OF DETERMINING MECHANISMS

There are a number of commonly used methods for determining mechanisms.[3] In most cases one method is not sufficient, and the problem is generally approached from several directions.

Identification of Products.[4] Obviously any mechanism proposed for a reaction must account for all the products obtained and for their relative proportions, including products formed by side reactions. Incorrect mechanisms for the von Richter reaction (**3-26,** p. 514) were accepted for many years because it was not realized that nitrogen was a major product. A proposed mechanism cannot be correct if it fails to predict the products in approximately their correct proportions. Any mechanism for the reaction

$$CH_4 + Cl_2 \xrightarrow{h\nu} CH_3Cl$$

which fails to account for the formation of a small amount of ethane cannot be correct (see reaction **4-1,** p. 532).

Determination of the Presence of an Intermediate.[5] In many reactions, intermediates are postulated. There are several ways, none of them foolproof, for attempting to learn whether or not an intermediate is present and, if so, the structure of the intermediate.

1. *Isolation of an intermediate.* It is sometimes possible to isolate an intermediate from a reaction mixture by stopping the reaction after a short time, or by the use of very mild conditions. For example, in the reaction

$$RCONH_2 + NaOBr \longrightarrow RNH_2$$

the intermediate RCONHBr has been isolated (see reaction **8-15,** p. 816). Such isolation is strong evidence that the reaction involves that intermediate, but it is not conclusive, since the compound may arise by an alternate path.

2. *Detection of an intermediate.* In many cases an intermediate cannot be isolated but can be detected by infrared, nuclear-magnetic-resonance, or other spectra. The detection, by Raman spectra, of NO_2^+ was regarded as strong evidence that this is an intermediate in the nitration of benzene (see reaction **1-2,** p. 396). Free-radical intermediates may often be detected by electron paramagnetic resonance.

3. *Trapping of an intermediate.* In some cases, the suspected intermediate is known to be one which reacts in a given way with a certain compound.

---

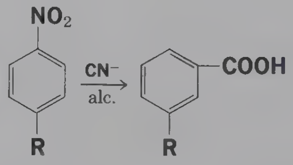
[3] For a treatise on this subject, see Friess, Lewis, and Weissberger, "Investigation of Rates and Mechanisms of Reactions," vol. VIII of Weissberger, "Technique of Organic Chemistry," 2d ed., two parts, Interscience Publishers, Inc., New York, 1961.

[4] The product criterion of mechanism is discussed by Lewis and Boozer in Ref. 3, part 2, pp. 1407–1426.

[5] Evidence for the formation of intermediates is discussed by Bender, in Ref. 3, part 2, pp. 1427–1517.

The intermediate may then be detected by running the reaction in the presence of that compound. For example, benzynes (p. 493) react with dienes in the Diels-Alder reaction (reaction **5-34,** p. 626). In any reaction where a benzyne is a suspected intermediate, the addition of a diene and the detection of the Diels-Alder adduct indicate that the benzyne was probably present.

4. *Addition of a suspected intermediate.* If a certain intermediate is suspected and if it can be obtained by other means, then under the same reaction conditions, it should give the same products. This kind of experiment can provide conclusive negative evidence: if the same products are not obtained, then the suspected compound is not an intermediate. However, if the correct products are obtained, this is not conclusive, since they may arise by coincidence. The von Richter reaction (**3-26,** p. 514) provides us with a good example here too.



For many years it had been assumed that an aryl cyanide was an intermediate, since cyanides are easily hydrolyzed to carboxylic acids (reaction **6-5,** p. 660). In fact, in 1954, *p*-chlorobenzonitrile was shown to give *p*-chlorobenzoic acid under the normal von Richter conditions.[6] However, when the experiment was repeated with 1-cyanonaphthalene, no 1-naphthoic acid was obtained, although 2-nitronaphthalene gave 13% 1-naphthoic acid under the same conditions.[7] This proved that 2-nitronaphthalene must have been converted to 1-naphthoic acid by a route which did not involve 1-cyanonaphthalene. It also showed that even the conclusion that *p*-chlorobenzonitrile was an intermediate in the conversion of *m*-nitrochlorobenzene to *p*-chlorobenzoic acid must now be suspected, since it is not likely that the mechanism would substantially change in going from the naphthalene to the benzene system.

The Study of Catalysis. Much information about the mechanism of a reaction may be obtained from a knowledge of which substances catalyze the reaction, which inhibit it, and which do neither. Of course, just as a mechanism must be compatible with the products, so must it be compatible with its catalysts.

Isotopic Labeling.[8] Much useful information has been obtained by using molecules which have been isotopically labeled and tracing the path of the reaction in that way. For example, in the reaction

---

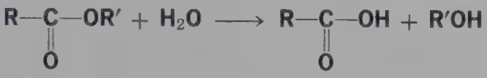
[6] Bunnett, Rauhut, Knutson, and Bussell, *J. Am. Chem. Soc.* **76,** 5755 (1954).

[7] Bunnett and Rauhut, *J. Org. Chem.* **21,** 944 (1956).

[8] For reviews, see Collins, *Advan. Phys. Org. Chem.* **2,** 3–91 (1964); Arnstein and Bentley, *Quart. Rev.* (*London*) **4,** 172–194 (1950); Saunders, in Ref. 3, part 2, pp. 1519–1548.

$$RCOO^- + BrCN \longrightarrow RCN$$

does the CN group in the product come from the CN in the BrCN? The use of ^{14}C supplied the answer, since $R^{14}CO_2^-$ gave *radioactive* RCN.[9] This surprising result saved a lot of labor, since it ruled out a mechanism involving the replacement of CO_2 by CN (see reaction **6-60**, p. 719). Other radioactive isotopes are also frequently used as tracers, but even stable isotopes may be used. An example is the hydrolysis of esters.



$$R-\underset{\underset{O}{\|}}{C}-OR' + H_2O \longrightarrow R-\underset{\underset{O}{\|}}{C}-OH + R'OH$$

Which bond of the ester is broken: the acyl—O or the alkyl—O bond? The answer is found by the use of $H_2{}^{18}O$. If the acyl—O bond breaks, then the labeled oxygen will appear in the acid; otherwise it will be in the alcohol (see reaction **0-11**, p. 309). Although neither compound is radioactive, the one which contains ^{18}O may be determined by submitting each to mass spectrometry. In a similar way, deuterium may be used as a label for hydrogen. In this case it is not necessary to use mass spectrometry, since infrared and nuclear-magnetic-resonance spectra may be used to determine when deuterium has been substituted for hydrogen.

In the labeling technique, it is not generally necessary to use completely labeled compounds. Partially labeled material is usually sufficient. There are some reactions, *exchange reactions,* which cannot be studied by any method which does not involve labeling, for example,[10]

$$C_4H_9Br + {}^*Br^- \longrightarrow C_4H_9{}^*Br + Br^-$$

Stereochemical Evidence.[11] If the products of a reaction are capable of existing in more than one stereoisomeric form, which form is obtained may give information about the mechanism. For example, (+)-malic acid was discovered by Walden[12] to give (−)-chlorosuccinic acid when treated with PCl_5, and the (+) enantiomer when treated with $SOCl_2$, showing that the mechanisms of these apparently similar conversions could not be the same (see pp. 253 and 269). Much useful information has been obtained about nucleophilic substitution, elimination, rearrangement, and addition reactions from this type of experiment. The isomers involved need not be enantiomers.

---

[9] Douglas, Eccles, and Almond, *Can. J. Chem.* **31,** 1127 (1953); Douglas and Burditt, *Can. J. Chem.* **36,** 1256 (1958).

[10] For a review, see Gold and Satchell, *Quart. Rev.* (*London*) **9,** 51–72 (1955).

[11] For lengthy treatments of the relationship between stereochemistry and mechanism, see Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, New York, 1962; Newman, "Steric Effects in Organic Chemistry," John Wiley & Sons, Inc., New York, 1956; and Friess, in Ref. 3, part 2, pp. 1549–1582.

[12] Walden, *Ber.* **29,** 136 (1896), **30,** 3149 (1897), **32,** 1833 (1899).

Thus, the fact that *cis*-2-butene, when treated with $KMnO_4$, gives *meso*-2,3-butanediol and not the racemic mixture, is evidence that the two OH groups attack the double bond from the same side (see reaction **5-28**, p. 616).

Kinetic Evidence.[13] The rate of a homogeneous reaction[14] is the rate of disappearance of a reactant or of appearance of a product. The rate nearly always changes with time, since it is usually proportional to concentration, and the concentration of reactants decreases with time. However, the rate is not always proportional to the concentration of all reactants, and a study of which reactants affect the rate often tells a good deal about the mechanism.

If the rate is proportional to the change in concentration of only one reactant (A), the rate law (the rate of change of concentration of A with time t) is

$$\text{Rate} = \frac{-d[\text{A}]}{dt} = k[\text{A}]$$

where k is the *rate constant* for the reaction. There is a minus sign because the concentration of A decreases with time. A reaction which follows such a rate law is called a *first-order reaction.* The units of k for a first-order reaction are sec^{-1}. The rate of a *second-order reaction* is proportional to the concentration of two reactants, or to the square of the concentration of one:

$$\frac{-d[\text{A}]}{dt} = k[\text{A}][\text{B}] \qquad \text{or} \qquad \frac{-d[\text{A}]}{dt} = k[\text{A}]^2$$

For a second-order reaction the units are liters mole^{-1} sec^{-1} or some other units expressing the reciprocal of concentration or pressure per unit time interval.

Similar expressions may be written for third-order reactions. A reaction whose rate is proportional to [A] and to [B] is said to be first order in A and in B, second order overall. A reaction rate may be measured in terms of any reactant or product, but the rates so determined are not necessarily the same. For example, if the stoichiometry of a reaction is

$$\mathbf{2A + B \longrightarrow C + D}$$

then, on a molar basis, A must disappear twice as fast as B, so that $-d[\text{A}]/dt$ and $-d[\text{B}]/dt$ are not equal, but the former is twice as large as the latter.

The rate law of a reaction (which is an experimentally determined fact) may or may not be related to the *molecularity,* which may be defined as the number of molecules which come together to form the activated complex. For reactions which take place in one step (reactions without an intermediate) the order is the same as the molecularity. A first-order one-step reaction is always unimolecular; a one-step reaction which is second order in A always involves two molecules of A; if it is first order in A and in B, then a molecule of A reacts with one of B, etc. For reactions which take place in more than one step, the order *for each step* is the same as the molecularity *for that step*. This fact enables us to predict the rate law for any proposed mechanism, although the calculations may at times get lengthy. If any one step of a mechanism is considerably slower than all the others (this is usually the case), then the rate of the overall reaction is essentially the same as that of the slow step, which is consequently called the *rate-determining* step.

---

[13] For the use of kinetics in determining mechanisms, see Frost and Pearson, "Kinetics and Mechanism," 2d ed., John Wiley & Sons, Inc., New York, 1961; Leffler and Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, 1963; and Ref. 3.

[14] A homogeneous reaction occurs in one phase. Heterogeneous kinetics have been studied much less.

For reactions which take place in two or more steps, we may distinguish between two broad cases:

1. The case where the first step is slower than any subsequent step and is consequently rate-determining. In such cases, the rate law simply includes the reactants which participate in the slow step. For example, if the reaction

$$\mathrm{A} + 2\mathrm{B} \longrightarrow \mathrm{C}$$

has the following mechanism:

$$\mathrm{A} + \mathrm{B} \xrightarrow{\text{slow}} \mathrm{I}$$

$$\mathrm{I} + \mathrm{B} \xrightarrow{\text{fast}} \mathrm{C}$$

where I is an intermediate, then the reaction is second order, with the rate law

$$\text{Rate} = \frac{-d[\mathrm{A}]}{dt} = k[\mathrm{A}][\mathrm{B}]$$

2. When the first step is not rate-determining, determination of the rate law is usually much more complicated. For example, consider the mechanism

$$1. \qquad \mathrm{A} + \mathrm{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{I}$$

$$2. \qquad \mathrm{I} + \mathrm{B} \xrightarrow{k_2} \mathrm{C}$$

where the first step is a rapid attainment of equilibrium, followed by a slow reaction to give C. The rate of disappearance of A is

$$\frac{-d[\mathrm{A}]}{dt} = k_1[\mathrm{A}][\mathrm{B}] - k_{-1}[\mathrm{I}]$$

Both terms must be included because A is being formed by the reverse reaction, as well as being used up by the forward reaction. This equation is of very little help as it stands, since we cannot measure the concentration of the intermediate. However, the combined rate law for the formation and disappearance of I is

$$\frac{d[\mathrm{I}]}{dt} = k_1[\mathrm{A}][\mathrm{B}] - k_{-1}[\mathrm{I}] - k_2[\mathrm{I}][\mathrm{B}]$$

At first glance we seem to be no better off with this equation, but we may make the assumption that *the concentration of I does not change with time,* since it is an intermediate which is used up (going either to A + B or to C) as fast as it is formed. This assumption, called the assumption of the *steady state,* enables us to set $d[\mathrm{I}]/dt$ equal to zero and hence to solve for [I] in terms of the measurable quantities [A] and [B].

$$[\mathrm{I}] = \frac{k_1[\mathrm{A}][\mathrm{B}]}{k_2[\mathrm{B}] + k_{-1}}$$

We may now insert this value for [I] into the original rate expression to obtain

$$\frac{-d[\mathrm{A}]}{dt} = \frac{k_1k_2[\mathrm{A}][\mathrm{B}]^2}{k_2[\mathrm{B}] + k_{-1}}$$

Note that this rate law is valid whatever the values of k_1, k_{-1}, and k_2. However, our original hypothesis was that the first step was faster than the second, or that

$$k_1[\mathrm{A}][\mathrm{B}] \gg k_2[\mathrm{I}][\mathrm{B}]$$

Since the first step is an equilibrium

$$k_1[\mathrm{A}][\mathrm{B}] = k_{-1}[\mathrm{I}]$$

so that

$$k_{-1}[\mathrm{I}] \gg k_2[\mathrm{I}][\mathrm{B}]$$

Canceling [I], we get

$$k_{-1} \gg k_2[\mathrm{B}]$$

We may thus neglect $k_2[\mathrm{B}]$ in comparison with k_{-1} and obtain

$$\frac{-d[\mathrm{A}]}{dt} = \frac{k_1k_2}{k_{-1}}[\mathrm{A}][\mathrm{B}]^2$$

The overall rate is thus third order: first order in A and second order in B. Incidentally, if the first step is rate-determining (as was the case in the preceding paragraph), then

$$k_2[\mathrm{B}] \gg k_{-1}$$

and

$$\frac{-d[\mathrm{A}]}{dt} = k_1[\mathrm{A}][\mathrm{B}]$$

which is the same rate law we deduced from the rule that where the first step is rate-determining, the rate law includes the reactants which participate in that step.

It is possible for a reaction to involve A and B in the rate-determining step, although only [A] appears in the rate law. This occurs when a large excess of B is present, say one hundred times the molar quantity of A. In this case the complete reaction of A uses up only 1 mole of B, leaving 99 moles. It is not easy to measure the change in concentration of B with time in such a case, and it is seldom attempted, especially when *B* is also the solvent. Since [B] is, for practical purposes, unchanging with time in such a case, the reaction appears to be first order in A, though actually both A and B are involved in the rate-determining step. This is often referred to as a *pseudo-first-order* reaction. Pseudo-order reactions may also come about when one reactant is a catalyst whose concentration does not change with time because it is replenished as fast as it is used up and when a reaction is conducted in a medium which keeps the concentration of a reactant constant, for example, in a buffer solution where H^+ or OH^- is a reactant.

What is actually being measured is the change in concentration of a product or a reactant with time. Many methods have been used to make such measurements. The choice of a method depends on its convenience and on its applicability to the reaction being studied. Among the most common methods are:[15]

1. *Periodic spectral readings.* In many cases the reaction may be carried out in the cell while it is in the instrument. Then all that is necessary is that the instrument be periodically read. Among the methods used are infrared and ultraviolet spectroscopy, nuclear magnetic resonance, and electron paramagnetic resonance (see Chapter 6).
2. *Quenching and analyzing.* A series of reactions may be set up, and each stopped in some way (perhaps by suddenly lowering the temperature, or adding an inhibitor) after a different amount of time has elapsed. The materials are then analyzed, by spectral readings, titrátions, gas chromatography, polarimetry (if optically active), or any other method.
3. *Removal of aliquots at intervals.* Each aliquot is then analyzed as in method 2.
4. *Dilatometry.* The change in total volume of a solution may be measured.

---

[15] For a discussion of methods used in solution, see Morse, in Ref. 3, part 1, pp. 499–578. For methods in the gas phase, see Maccoll, in Ref. 3, part 1, pp. 427–498.

5. Measurement of changes in total pressure, for gas-phase reactions.

6. *Calorimetric methods.* The output or absorption of heat may be measured at time intervals.

Special methods exist for very fast reactions.[16]

In any case what is usually obtained is a graph showing how a concentration varies with time. This must be interpreted[17] so as to obtain a rate law and a value of k. If a reaction obeys simple first- or second-order kinetics, the interpretation is generally not difficult. For example, if the concentration at the start is A_0, then the first-order rate law

$$\frac{-d[\mathrm{A}]}{dt} = k[\mathrm{A}] \qquad \text{or} \qquad \frac{-d[\mathrm{A}]}{[\mathrm{A}]} = k\,dt$$

may be integrated between the limits $t = 0$ and $t = t$ to give

$$-\ln \frac{[\mathrm{A}]}{\mathrm{A}_0} = kt$$

or

$$\ln [\mathrm{A}] = -kt + \ln \mathrm{A}_0$$

Therefore, if a plot of ln [A] against t is linear, the reaction is first order, and k may be obtained from the slope. For first-order reactions it is customary to express the rate not only by the rate constant k, but also by the *half-life,* which is the time required for half of any given quantity of a reactant to be used up. Since the half-life ($t_{1/2}$) is the time required for [A] to reach $\mathrm{A}_0/2$, we may say that

$$\ln \left(\frac{\mathrm{A}_0}{2}\right) = -kt_{1/2} + \ln \mathrm{A}_0$$

so that

$$t_{1/2} = \frac{\ln \left(\dfrac{\mathrm{A}_0}{\mathrm{A}_0/2}\right)}{k} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

For the general case of a reaction first order in A and first order in B, second order overall, integration is complicated, but it may be simplified if equimolar amounts of A and B are used, so that $\mathrm{A}_0 = \mathrm{B}_0$. In this case

$$\frac{-d[\mathrm{A}]}{dt} = k[\mathrm{A}][\mathrm{B}]$$

is equivalent to

$$\frac{-d[\mathrm{A}]}{dt} = k[\mathrm{A}]^2 \qquad \text{or} \qquad \frac{-d[\mathrm{A}]}{[\mathrm{A}]^2} = k\,dt$$

---

[16] See Ref. 3, part 2.

[17] For a discussion, much fuller than is given here, of methods for interpreting kinetic data, see Livingston, in Ref. 3, part 1, pp. 109–175; and Frost and Pearson, Ref. 2, pp. 8–55.

Integrating as before,

$$\frac{1}{[A]} - \frac{1}{A_0} = kt$$

Thus, under equimolar conditions, if a plot of $1/[A]$ against t is linear, the reaction is second order, with a slope of k. It is obvious that the same will hold true for a reaction second order in A.

Although many reaction-rate studies do give linear plots, which can therefore be easily interpreted, the results in many other studies are not so simple. In some cases a reaction may be first order at low concentrations but second order at higher concentrations. In other cases fractional orders are obtained, and even negative orders. The interpretation of complex kinetics often requires much skill and effort.

Several types of mechanistic information may be obtained from kinetic studies.

1. From the order of a reaction, information may be obtained about which molecules and how many take part in the rate-determining step. Such knowledge is very useful and often essential in elucidating a mechanism. Erroneous ideas about the mechanism of the benzidine rearrangement (reaction **8-24**, p. 828) were accepted for many years, until it was discovered that the reaction was usually second order in H^+ (third order overall), indicating that *two* protons were required in the rate-determining step. However, it is often difficult to relate the order of a reaction to the mechanism, especially when the order is fractional or negative. In addition, it is frequently the case that two or more proposed mechanisms for a reaction are kinetically indistinguishable, that is, they predict the same rate law.
2. Probably the most useful data obtained kinetically are the rate constants themselves. These are important, since they may tell us the effect on the rate of a reaction of changes in the structure of the reactants (see Chapter 9), the solvent, the ionic strength, the addition of catalysts, etc.
3. If the rate is measured at several temperatures, then in most cases, a plot of $\ln k$ against $1/T$ (T stands for absolute temperature) is nearly linear, with a negative slope, and fits the equation

$$\ln k = \frac{-E_a}{RT}$$

where R is the gas constant. This permits calculation of E_a, which is the Arrhenius activation energy of the reaction. From this may be obtained $\Delta H^{\ddagger}$ by

$$E_a = \Delta H^{\ddagger} + RT$$

Isotope Effects. When a hydrogen in a reactant molecule is replaced by deuterium, there is often a change in the rate. Such changes are known as

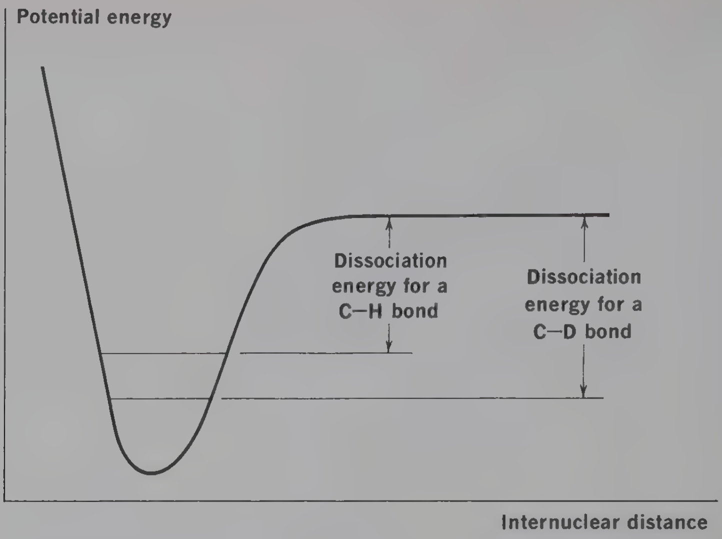


Figure 3. *A* C—D *bond vibrates at a lower energy than does a corresponding* C—H *bond, thus the dissociation energy is higher.*

deuterium isotope effects[18] and are expressed by the ratio k_H/k_D. The ground-state vibrational energy (called the zero-point vibrational energy) of a bond depends on the mass of the atoms involved and is lower when the reduced mass is higher.[19] Therefore, D—C, D—O, D—N bonds, etc., have lower energies in the ground state than the corresponding H—C, H—O, H—N bonds, etc. Complete dissociation of a deuterium bond therefore requires more energy than that for a corresponding hydrogen bond in the same environment (Figure 3). If an H—C, H—O, or H—N bond is not broken at all in a reaction, or is broken in a non-rate-determining step, then substitution of deuterium for hydrogen causes no change in the rate (see p. 215 for an exception to this statement), but if the bond is broken in the rate-determining step, then the rate must be lowered by the substitution.

This provides a valuable diagnostic tool for determination of mechanism. For example, in the bromination of acetone (reaction **2-4,** p. 458)

$$CH_3COCH_3 + Br_2 \longrightarrow CH_3COCH_2Br$$

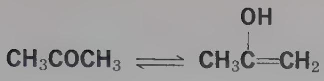
the fact that the rate is independent of the bromine concentration led to the postulate that the rate-determining step was tautomerization of the acetone.

---

[18] For a monograph, see Melander, "Isotope Effects on Reaction Rates," The Ronald Press Company, New York, 1960. For reviews, see Saunders, *Surv. Progr. Chem.* **3,** 109–146 (1966); Westheimer, *Chem. Rev.* **61,** 265–273 (1961); Wiberg, *Chem. Rev.* **55,** 713–743 (1955); Saunders, in Ref. 3, part 1, pp. 389–425; and Thornton, "Solvolysis Mechanisms," pp. 194–229, The Ronald Press Company, New York, 1964.

[19] The reduced mass μ of two atoms connected by a covalent bond is

$$\mu = \frac{m_1 m_2}{m_1 + m_2}$$



$$CH_3COCH_3 \rightleftharpoons CH_3\overset{OH}{C}{=}CH_2$$

In turn, the rate-determining step of the tautomerization involves cleavage of a C—H bond (see reaction **2-3**, p. 457). Thus there should be a substantial isotope effect if deuterated acetone is brominated. In fact, k_H/k_D was found to be about 7.[20] Deuterium isotope effects range from 1 (no isotope effect at all) to about 8 or 9.

The substitution of tritium for hydrogen gives isotope effects which are numerically larger.[21] Isotope effects have also been observed with other elements, but they are much smaller, about 1.02 to 1.10. For example, $k_{^{12}C}/k_{^{13}C}$ for

$$Ph^*CH_2Br + CH_3O^- \xrightarrow{CH_3OH} Ph^*CH_2OCH_3$$

is 1.053.[22] Although they are small, heavy-atom isotope effects can be measured quite accurately and are often very useful.

Deuterium isotope effects have been found even where it is certain that the C—H bond does not break at all in the reaction. Such effects are called *secondary isotope effects*,[23] the term *primary isotope effect* being reserved for the type discussed previously. Secondary isotope effects may be divided, for convenience, into α and β effects, although it is possible that they have the same cause. In a β secondary isotope effect, substitution of deuterium for hydrogen β to the position of bond breaking slows the reaction. An example is solvolysis of isopropyl bromide:

$$(CH_3)_2CHBr + H_2O \xrightarrow{k_H} (CH_3)_2CHOH$$

$$(CD_3)_2CHBr + H_2O \xrightarrow{k_D} (CD_3)_2CHOH$$

where k_H/k_D was found to be 1.34.[24] The cause of β isotope effects has been a matter of much controversy, but they are most likely due to hyperconjugation effects in the transition state. The effects are greatest when the transition state has considerable carbonium-ion character.[25] Although the C—H bond in question is not broken in the transition state, the carbonium ion is stabilized by hyperconjugation involving this bond. Because of hyperconjugation, the difference in vibrational energy between the C—H bond and the C—D bond in the transition state is less than it is in the ground state, so that the reaction is slowed by substitution of deuterium for hydrogen.

---

[20] Reitz and Kopp, *Z. physik. Chem.* **A184**, 429 (1939).

[21] Swain, Stivers, Reuwer, and Schaad, *J. Am. Chem. Soc.* **80**, 5885 (1958). For a review of tritium isotope effects, see Yakushin, *Russ. Chem. Rev.* **31**, 123–131 (1962).

[22] Stothers and Bourns, *Can. J. Chem.* **40**, 2007 (1962).

[23] For reviews, see Laszlo and Welvart, *Bull. Soc. chim. France* **1966**, 2412–2438; Halevi, *Progr. Phys. Org. Chem.* **1**, 109–221 (1963); and Shiner, Mahler, Baker, and Hiatt, *Ann. N.Y. Acad. Sci.* **84**, 583–595 (1960).

[24] Leffek, Llewellyn, and Robertson, *Can. J. Chem.* **38**, 2171 (1960).

[25] Bender and Feng, *J. Am. Chem. Soc.* **82**, 6318 (1960); Jones and Bender, *J. Am. Chem. Soc.* **82**, 6322 (1960).

Support for hyperconjugation as the major cause of β isotope effects is the fact that the effect is greatest when D is trans to the leaving group[26] (because of the requirement that all atoms in a resonance system be coplanar, planarity of the D—C—C—X system would most greatly decrease the hyperconjugation), and the fact that secondary isotope effects can be transmitted through unsaturated systems.[27] However, β isotope effects have also been attributed to inductive effects (CD_3 is apparently a better electron donor than CH_3),[28] vibrational effects,[29] and other causes.[30] Part of the difficulty in attempting to explain these effects is their small size, ranging only as high as 1.5. Another complicating factor is that they may change with temperature. In one case[31] k_H/k_D was 1.00 ± 0.01 at 0°, 0.90 ± 0.01 at 25°, and 1.15 ± 0.09 at 65°. Whatever the cause, there seems to be a good correlation between β secondary isotope effects and carbonium character in the transition state, and they are thus a useful tool for probing mechanisms.

The other type of secondary isotope effect results from a replacement of hydrogen by deuterium at the carbon containing the leaving group. These (called α secondary isotope effects) are varied, values so far reported ranging from 0.94 to 1.16. These effects are also correlated with carbonium-ion character. A straight-line relationship has been reported between the size of the α isotope effect and the amount of carbonium-ion character in the transition state.[32] However, exceptions to this have been reported.[33] The accepted explanation for α isotope effects is that one of the bending C—H vibrations is affected by the substitution of D for H more or less strongly in the transition state than in the ground state.[34] Depending on the nature of the transition state, this may increase or decrease the rate of the reaction. γ secondary isotope effects have also been reported.[35]

Another kind of isotope effect is the solvent isotope effect.[36] Reactions catalyzed by acid are usually faster in D_2O than in H_2O. A number of explanations have been suggested for this.[37]

The methods described in this chapter are not the only means of determining mechanisms. In an attempt to elucidate a mechanism, the investigator is limited only by his ingenuity.

---

[26] Shiner, Murr, and Heinemann, *J. Am. Chem. Soc.* **85**, 2413 (1963); Shiner and Humphrey, *J. Am. Chem. Soc.* **85**, 2416 (1963); Shiner and Jewett, *J. Am. Chem. Soc.* **86**, 945 (1964).

[27] Shiner and Kriz, *J. Am. Chem. Soc.* **86**, 2643 (1964).

[28] Halevi, Nussim, and Ron, *J. Chem. Soc.* **1963**, 866; Halevi and Nussim, *J. Chem. Soc.* **1963**, 876.

[29] Weston, *Tetrahedron* **6**, 31 (1959).

[30] Bartell, *J. Am. Chem. Soc.* **83**, 3567 (1961); Leffek, Robertson, and Sugamori, *Can. J. Chem.* **39**, 1989 (1961).

[31] Halevi and Margolin, *Proc. Chem. Soc.* **1964**, 174.

[32] Hartman and Robertson, *Can. J. Chem.* **38**, 2033 (1960).

[33] Leffek, *Can. J. Chem.* **42**, 851 (1964).

[34] Streitwieser, Jagow, Fahey, and Suzuki, *J. Am. Chem. Soc.* **80**, 2326 (1958).

[35] Leffek, Llewellyn, and Robertson, *J. Am. Chem. Soc.* **82**, 6315 (1960); *Chem. Ind.* (*London*) **1960**, 588.

[36] For a discussion, see Purlee, *J. Am. Chem. Soc.* **81**, 263 (1959); Long, *Ann. N.Y. Acad. Sci.* **84**, 596–602 (1960).

[37] Heppolette and Robertson, *J. Am. Chem. Soc.* **83**, 1834 (1961); Bunton and Shiner, *J. Am. Chem. Soc.* **83**, 3207 (1961); Ref. 36.

CHAPTER EIGHT
Acids and Bases

Two acid-base theories are in use today in organic chemistry: the Brönsted theory and the Lewis theory.[1] These theories are quite compatible, and are used for different purposes.[2]

Brönsted Theory. According to this theory, an acid is defined as a *proton donor* and a base as a *proton acceptor* (a base must have available a pair of electrons to share with the proton; this is usually present as an unshared pair, but sometimes is in a π orbital). An acid-base reaction is simply the transfer of a proton from an acid to a base. When the acid gives up a proton, the species remaining still retains the electron pair to which the proton was formerly attached. Thus the new species, in theory at least, can reacquire a proton and is therefore a base. It is referred to as the *conjugate base* of the acid. All acids have a conjugate base, and all bases have a *conjugate acid.* All acid-base reactions fit the equation

$$\begin{array}{ccccc} \mathrm{A{-}H} + & \overline{\mathrm{B}} & \rightleftharpoons & \overline{\mathrm{A}} & + \mathrm{B{-}H} \\ \text{Acid}_1 & \text{Base}_2 & & \text{Base}_1 & \text{Acid}_2 \end{array}$$

No charges are shown in this equation, but an acid always has a charge which is one positive unit higher than that of its conjugate base, whether the charge on the acid is positive, negative, or neutral. Many substances can be both bases and acids. Such species are called *amphoteric.*

Acid strength may be defined as the tendency to give up a proton, and *base strength* as the tendency to accept a proton. Acid-base reactions occur because acids are not equally strong. If an acid, say HCl, is placed in contact with the conjugate base of a weaker acid, say acetate ion, the proton will be transferred, because the HCl has a greater tendency to lose its proton than does acetic acid. That is, the equilibrium

$$\mathrm{HCl} + \mathrm{CH_3COO^-} \rightleftharpoons \mathrm{CH_3COOH} + \mathrm{Cl^-}$$

lies well over to the right. On the other hand, treatment of acetic acid with chloride ion gives essentially no reaction, since the weaker acid already has the proton.

This is always the case for any two acids, and by measuring positions of the equilibrium the relative strengths of acids and bases may be determined.[3] Of course, if the two acids involved are close to one another in strength, a measurable reaction will occur from both sides, although the position of equilibrium will still be over to the side of the weaker acid (unless the acidities are equal within experimental limits). In this manner it is possible to construct a table in which acids are listed in order of acid strength (Table 1).[4] Next to each acid in Table 1 is shown its conjugate base. It is obvious that, if the acids in such a table are listed in *decreasing* order of acid strength, then the bases must be listed in *increasing* order of base strength, since the stronger the acid, the weaker must be its conjugate base. The pK_a values in Table 1 are most accurate in the middle of the table. They are much harder to measure for very strong and very weak acids,[5] and these values must be regarded as approximate. Qualitatively, it can be determined that $HClO_4$ is a stronger acid than H_2SO_4, since a mixture of $HClO_4$ and H_2SO_4 in methyl isobutyl ketone may be titrated to an $HClO_4$ endpoint without interference by H_2SO_4.[6] Similarly, $HClO_4$ can be shown to be stronger than HNO_3 or HCl. However, this is not quantitative, and the value of -10 in the table is not much more than an educated guess. The values for RNO_2H^+, $ArNO_2H^+$, HI, $RCNH^+$, and RSH_2^+ must also be regarded as highly speculative. Only for acids weaker than hydronium ion and stronger than water can very accurate values be obtained.

---

[1] For a monograph on acids and bases, see Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N.Y., 1959. For a review, see Gillespie, in Olah, "Friedel-Crafts and Related Reactions," vol. 1, pp. 169–199, Interscience Publishers, Inc., New York, 1963.

[2] For discussions of the historical development of acid-base theory, see Bell, Ref. 1, pp. 7–17; and Bell, *Quart. Rev.* (*London*) **1**, 113–125 (1947).

By the use of tables such as Table 1, it is possible to determine whether a given acid will react with a given base. For tables in which acids are listed in order of decreasing strength, the rule is that *any acid will react with any base in the table which is below it, but not with any above it.* The chart is most useful when the acid and the base are not close together, for the following reasons:

1. When an acid and a base are close together, the reaction will not be complete, though the position of equilibrium will be such that the weaker acid predominates.
2. The order can change with temperature. Thus, above 50° the order of base strength is $BuOH > H_2O > Bu_2O$; from 1 to 50°, the order is $BuOH > Bu_2O > H_2O$; while below 1°, it becomes $Bu_2O > BuOH > H_2O$.[7]
3. For acids stronger than hydronium ion and weaker than water, not only are the pK_a values uncertain, but in many cases so are the relative positions.

It must be emphasized that the order of acid strength in Table 1 applies when a given acid and base react without a solvent or, when possible, in

---

[3] Some acid-base reactions are slow, and in these cases time must be allowed for the system to come to equilibrium.

[4] Table 1 is a thermodynamic acidity scale and applies only to positions of equilibria. For the distinction between thermodynamic and kinetic acidity, see p. 143.

[5] For discussions of acidity of very weak acids, see Cram, "Fundamentals of Carbanion Chemistry," pp. 1–45, Academic Press Inc., New York, 1965; and Streitwieser and Hammons, *Progr. Phys. Org. Chem.* **3**, 41–80 (1965).

[6] Kolthoff and Bruckenstein, in Kolthoff and Elving, "Treatise on Analytical Chemistry," vol. 1, part 1, pp. 475–542, 479, Interscience Publishers, Inc., New York, 1959.

[7] Gerrard and Macklen, *Chem. Rev.* **59**, 1105–1123.

TABLE 1. pK_a values for many types of acids
The values in bold print are exact values. The others are approximate, especially above 18 and below −2[8]

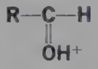
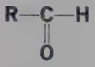
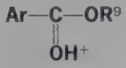
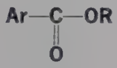
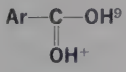
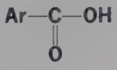
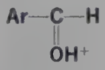
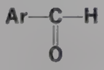
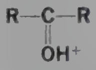
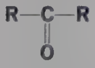
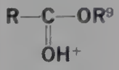
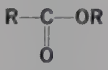
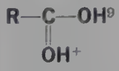
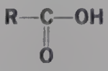
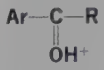
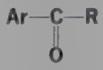
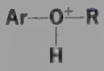
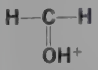
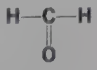
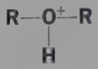
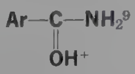
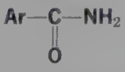
Acid	*Base*	*Approximate pK_a (relative to water)*	*Ref.*
RNO_2H^+	RNO_2	−12	13
$ArNO_2H^+$	$ArNO_2$	−11	13
$HClO_4$	ClO_4^-	−10	14
HI	I^-	−10	14
$RCNH^+$	RCN	−10	11
H_2SO_4	HSO_4^-		
 $\mathrm{R{-}\underset{\underset{\displaystyle OH^+}{\|}}{C}{-}H}$	 $\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}H}$	−8	13
 $\mathrm{Ar{-}\underset{\underset{\displaystyle OH^+}{\|}}{C}{-}OR}$[9]	 $\mathrm{Ar{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OR}$	−7.4	13
$ArSO_3H$	$ArSO_3^-$	−7	14
HCl	Cl^-	−7	14
$ArOH_2^+$	ArOH	−7	12
RSH_2^+	RSH	−7	14
 $\mathrm{Ar{-}\underset{\underset{\displaystyle OH^+}{\|}}{C}{-}OH}$[9]	 $\mathrm{Ar{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OH}$	−7	29
 $\mathrm{Ar{-}\underset{\underset{\displaystyle OH^+}{\|}}{C}{-}H}$	 $\mathrm{Ar{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}H}$	−7	30
 $\mathrm{R{-}\underset{\underset{\displaystyle OH^+}{\|}}{C}{-}R}$	 $\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R}$	−7	11
 $\mathrm{R{-}\underset{\underset{\displaystyle OH^+}{\|}}{C}{-}OR}$[9]	 $\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OR}$	−6.5	13
 $\mathrm{R{-}\underset{\underset{\displaystyle OH^+}{\|}}{C}{-}OH}$[9]	 $\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OH}$	−6	13
 $\mathrm{Ar{-}\underset{\underset{\displaystyle OH^+}{\|}}{C}{-}R}$	 $\mathrm{Ar{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R}$	−6	15, 30
 $\mathrm{Ar{-}\underset{\underset{\displaystyle H}{|}}{\overset{+}{O}}{-}R}$	Ar—O—R	−6	12, 16
 $\mathrm{H{-}\underset{\underset{\displaystyle OH^+}{\|}}{C}{-}H}$	 $\mathrm{H{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}H}$	−4	17
 $\mathrm{R{-}\underset{\underset{\displaystyle H}{|}}{\overset{+}{O}}{-}R}$	R—O—R	−3.5	11, 16, 18
$R_3COH_2^+$	R_3COH	−2	18
$R_2CHOH_2^+$	R_2CHOH	−2	18
$RCH_2OH_2^+$	RCH_2OH	−2	11, 19, 18
 $\mathrm{Ar{-}\underset{\underset{\displaystyle OH^+}{\|}}{C}{-}NH_2}$[9]	 $\mathrm{Ar{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}NH_2}$	−2	13
H_3O^+	H_2O	**−1.74**	

TABLE 1. *(Cont.)*

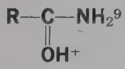
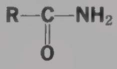
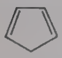
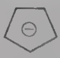
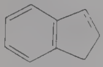
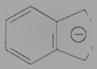
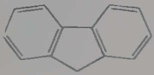
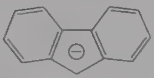
Acid	*Base*	*Approximate pK$_a$ (relative to water)*	*Ref.*
HNO_3	NO_3^-	−1.4	14
 $R-\underset{\overset{\|}{OH^+}}{C}-NH_2$[9]	 $R-\underset{\overset{\|}{O}}{C}-NH_2$	−1	11
HSO_4^-	$SO_4^=$	**1.99**	20
HF	F^-	**3.17**	20
$HONO$	NO_2^-	**3.29**	20
$ArNHR_2^+$	$ArNR_2$	3–5	21
$ArNH_3^+$	$ArNH_2$	3–5	21
$RCOOH$	$RCOO^-$	4–5	21
$HCOCH_2CHO$	$HCO\overset{\ominus}{\bar{C}}HCHO$	5	22
H_2CO_3[10]	HCO_3^-	**6.35**	20
H_2S	HS^-	**7.00**	20
$ArSH$	ArS^-	8	21
$CH_3COCH_2COCH_3$	$CH_3CO\overset{\ominus}{\bar{C}}HCOCH_3$	9	22
NH_4^+	NH_3	**9.24**	20
$ArOH$	ArO^-	9–11	21
RCH_2NO_2	$R\overset{\ominus}{\bar{C}}HNO_2$	10	23
R_3NH^+	R_3N	10–11	21
RNH_3^+	RNH_2	10–11	21
HCO_3^-	$CO_3^=$	10.33	20
$R_2NH_2^+$	R_2NH	11	21
CH_3COCH_2COOEt	$CH_3CO\overset{\ominus}{\bar{C}}HCOOEt$	11	22
RSH	RS^-	12	21
$NCCH_2CN$	$NC\overset{\ominus}{\bar{C}}HCN$	12	22
$EtOOCCH_2COOEt$	$EtOOC\overset{\ominus}{\bar{C}}HCOOEt$	13	22
$MeSO_2CH_2SO_2Me$	$MeSO_2\overset{\ominus}{\bar{C}}HSO_2Me$	14	22
		14–15	24
H_2O	OH^-	16	14
CH_3OH	CH_3O^-	16	25
RCH_2OH	RCH_2O^-	18	25
R_2CHOH	R_2CHO^-	18	25
$PhC{\equiv}CH$	$PhC{\equiv}C^-$	18.5	26
R_3COH	R_3CO^-	19	25
$ArCOCH_2R$	$ArCO\overset{\ominus}{\bar{C}}HR$	19	23
$RCOCH_2R$	$RCO\overset{\ominus}{\bar{C}}HR$	19–20	22, 25

TABLE 1. *(Cont.)*

Acid	*Base*	*Approximate pK_a (relative to water)*	*Ref.*
		20	27
		23	27
$\mathrm{ROOCCH_2R}$	$\mathrm{ROOC}\overset{\ominus}{\bar{\mathrm{C}}}\mathrm{HR}$	24.5	22
$\mathrm{RCH_2CN}$	$\mathrm{R}\overset{\ominus}{\bar{\mathrm{C}}}\mathrm{HCN}$	25	22
$\mathrm{RCONH_2}$	$\mathrm{RCONH^-}$	25	23
$\mathrm{HC{\equiv}CH}$	$\mathrm{HC{\equiv}C^-}$	25	26
$\mathrm{ArNH_2}$	$\mathrm{ArNH^-}$	25	28
$\mathrm{Ar_3CH}$	$\mathrm{Ar_3C^-}$	31.5	27
$\mathrm{Ar_2CH_2}$	$\mathrm{Ar_2CH^-}$	33	27
$\mathrm{MeSOCH_2R}$	$\mathrm{MeSO}\overset{\ominus}{\bar{\mathrm{C}}}\mathrm{HR}$	33.5	28
$\mathrm{NH_3}$	$\mathrm{NH_2^-}$	34	28
$\mathrm{ArCH_3}$	$\mathrm{ArCH_2^-}$	35	26
$\mathrm{CH_2{=}CH_2}$	$\mathrm{CH_2{=}CH^-}$	36.5	26
PhH	$\mathrm{Ph^-}$	37	26
cyclo-$\mathrm{C_3H_6}$	*cyclo*-$\mathrm{C_3H_5^-}$	39	26
$\mathrm{CH_4}$	$\mathrm{CH_3^-}$	40	26
$\mathrm{C_2H_6}$	$\mathrm{C_2H_5^-}$	42	26
$\mathrm{(CH_3)_2CH}$	$\mathrm{(CH_3)_2C^-}$	44	26
cyclo-$\mathrm{C_6H_{12}}$	*cyclo*-$\mathrm{C_6H_{11}^-}$	45	26

---

[8] In this table it has not been possible to give pK_a values for individual compounds (with a few exceptions), but only average values for functional groups. Extensive tables of pK values for many carboxylic and other acids and amines are given in Ref. 21. Kortüm, Vogel, and Andrussow, *Pure Appl. Chem.* **1,** 190–536 (1960), give values for 631 carboxylic acids and 110 phenols. Reference 13 gives hundreds of values for very strong acids (very weak bases). Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth & Co. (Publishers), Ltd., London, 1965, lists pK values for 3790 amines and other bases.

[9] Acids, esters, and amides are shown in this table to be protonated on the carbonyl oxygen. There has been some controversy on this point, but the weight of evidence today is in that direction. See Katritzky and Jones, *Chem. Ind. (London)* **1961,** 722; Ottenheym, van Raayen, Smidt, Groenwege, and Veerkamp, *Rec. trav. chim.* **80,** 1211 (1961); Stewart and Muenster, *Can. J. Chem.* **39,** 401 (1961); Stewart and Yates, *J. Am. Chem. Soc.* **82,** 4059 (1960); Berger, Loewenstein, and Meiboom, *J. Am. Chem. Soc.* **81,** 62 (1959); Fraenkel and Franconi, *J. Am. Chem. Soc.* **82,** 4478 (1960); and Casadevall, Cauquil, and Corriu, *Bull. Soc. chim. France* **1964,** 187.

[10] This value includes the CO_2 usually present. The value for H_2CO_3 alone is 3.9 (Ref. 14).

[11] Deno and Wisotsky, *J. Am. Chem. Soc.* **85,** 1735 (1963); Deno, Gaugler, and Wisotsky, *J. Org. Chem.* **31,** 1967 (1966).

[12] Arnett and Wu, *J. Am. Chem. Soc.* **82,** 5660 (1960).

[13] Arnett, *Progr. Phys. Org. Chem.* **1,** 223–403 (1963), pp. 324–325.

[14] Bell, Ref. 1.

water. In other solvents the order may be greatly different (see pp. 224 and 229).

Acids and Basic Solvents.[31] One way to determine the position of an acid in a table such as Table 1 is simply to measure the position of equilibrium with a number of appropriate bases. This method is not always easy in practice. Another way is to make use of an acidic or basic solvent. An acidic solvent (SH) may be used in the following manner: a base placed in such a solvent will take protons from the solvent if it is stronger than S^-. We may imagine two bases B_1 and B_2, which are weaker than S^-, and two others, B_3 and B_4, which are stronger. Then a list similar to Table 1 will be

HB_2^+	B_2
HB_1^+	B_1
SH	S^-
HB_3^+	B_3
HB_4^+	B_4

If the base is B_3 or B_4, then the concentrations of S^- and HB_3^+ (or HB_4^+) will be greater than those of SH and B_3 (or B_4). For B_1 and B_2 the reverse will be true. Now if the $[SH/S^-]$ or $[HB^+/B]$ ratios can be measured, this is a means of telling not only whether each B is stronger or weaker than S^-, but also whether B_1 is stronger or weaker than B_2. From these measurements quantitative scales can be set up.[32] When the solvent is water, this is the pK_b scale.

---

[15] Fischer, Griger, Packer, and Vaughan, *J. Am. Chem. Soc.* **83**, 4208 (1961).

[16] Arnett and Wu, *J. Am. Chem. Soc.* **82**, 4999 (1960).

[17] McTigue and Sime, *Australian J. Chem.* **16**, 592 (1963).

[18] Deno and Turner, *J. Org. Chem.* **31**, 1969 (1966).

[19] Newall and Eastham, *Can. J. Chem.* **39**, 1752 (1961).

[20] Bruckenstein and Kolthoff, in Kolthoff and Elving, "Treatise on Analytical Chemistry," vol. 1, part 1, pp. 432–433, Interscience Publishers, Inc., New York, 1959.

[21] Brown, McDaniel, and Häflinger, in Braude and Nachod, "Determination of Organic Structures by Physical Methods," vol. 1, pp. 567–662, Academic Press Inc., New York, 1955.

[22] Pearson and Dillon, *J. Am. Chem. Soc.* **75**, 2439 (1953).

[23] Cram, *Chem. Eng. News* **41**, No. 33, 94 (Aug. 19, 1963).

[24] Dessy, Okuzumi, and Chen, *J. Am. Chem. Soc.* **84**, 2899 (1962).

[25] McEwen, *J. Am. Chem. Soc.* **58**, 1124 (1936).

[26] Cram, "Fundamentals of Carbanion Chemistry," p. 19, Academic Press Inc., New York, 1965. Also see Dessy, Kitching, Psarras, Salinger, Chen, and Chivers, *J. Am. Chem. Soc.* **88**, 460 (1966).

[27] Streitwieser, Ciuffarin, and Hammons, *J. Am. Chem. Soc.* **89**, 63 (1967).

[28] These values are based on those of Ref. 23, but corrected to the newer scales of Ref. 26.

[29] Stewart and Granger, *Can. J. Chem.* **39**, 2508 (1961).

[30] Yates and Stewart, *Can. J. Chem.* **37**, 664 (1959); Stewart and Yates, *J. Am. Chem. Soc.* **80**, 6355 (1958).

[31] For a fuller treatment, see Kolthoff, in Kolthoff and Elving, "Treatise on Analytical Chemistry," vol. 1, part 1, pp. 407–420, Interscience Publishers, Inc., New York, 1959.

[32] Actually, [SH/S] cannot be accurately measured, since the amount of SH is overwhelming. But if $[S^-]$ can be accurately measured, then the value of $[BH^+]$ is known, since it must be equal to [S]. If the initial concentration (B_0) of B was known, this gives the $[HB^+/B]$ ratio, since $B_0 = [B] + [BH^+]$.

However, if two bases, say B_3 and B_4, are so strong that $[HB_3^+/B_3]$ and $[HB_4^+/B_4]$ are both greater than, say, 100, then all that can be said is that they are both essentially completely protonated, and it is not possible to tell the difference between a ratio of, say, 10^3 and one of 10^6. This is called the *leveling effect* of the solvent, since, to the solvent SH, the bases B_3 and B_4 are equally strong, even though their actual strengths may be greatly different. Similarly, if the two bases are so weak in relation to SH that the two ratios are both less than, say, $\frac{1}{100}$, the solvent cannot distinguish between their basicities. A similar argument holds for basic solvents.

In water, which is both an acidic and a basic solvent, it is very easy to measure S^- accurately (or SH^+ for measuring acid strengths), since H_3O^+ (and consequently OH^-) may be quite accurately measured between about 10 and 10^{-15} moles/liter; hence the pK of acids stronger than water and weaker than hydronium ion can be accurately determined. But outside this range, water is useless as a solvent because of two kinds of leveling effect. When an acid is stronger than H_3O^+, then it is converted essentially completely to H_3O^+. One mole each of two strong acids will give, say, 0.9990 mole H_3O^+ and 0.9999 mole H_3O^+. It is not possible to tell the difference, since the activity is what is actually being measured, and the difference between activity and concentration is greater than the difference between 0.9990 and 0.9999. The second kind of leveling effect is found with acids weaker than water, since the amount of H_3O^+ produced by the acid is less than that produced by the autoprotolysis of the water and thus cannot be measured. Another way of saying this is that the base water would rather take a proton from the acid water than from an acid weaker than water. Similarly, in water, pK_b can be measured only for bases stronger than water and weaker than OH^-.

Other amphoteric solvents may be used in a similar manner to measure other areas of the chart. In acetic acid, it is possible to distinguish acidities of acids which in water would have pK_a between about -10 and $+5$. That is, in acetic acid, it is possible to distinguish HBr and HCl, but not H_2O and phenol. Conversely, in ammonia, the carboxylic acids are as strong as HCl, while the acidities of methanol and ethanol may be differentiated. The pK_a range in this solvent, relative to water, is about 3 to 23. In solvents such as these, we must measure, not $[H_3O^+]$ or $[OH^-]$, but analogously, $[CH_3COOH_2^+]$ or $[CH_3COO^-]$, or $[NH_4^+]$ or $[NH_2^-]$. These are usually much more difficult to measure than pH. Therefore many methods have been devised, e.g., freezing-point depressions, infrared spectra, vapor-pressure measurements, etc.; still the values obtained are seldom as accurate as values in water. Of course, values obtained in other solvents must be corrected to the water scale. As a first approximation, this may be done by simple subtraction, if the pK_a of any acid is known in both water and the other solvent, since differences in pK values of two acids of the same charge type should not be greatly affected by the solvent. However, when acids of different charge types are compared, there are no simple correlations.

Solvents which are not amphoteric may also be used. For basic solvents, such as diethyl ether or pyridine, there is a limit only on the strong-acid side, since on the weak-acid side there is no autoprotolysis to supply Et_2OH^+ or

$C_5H_5NH^+$ to compete with that formed from even a weak acid and the solvent. Similarly, for acidic solvents such as HCN, there is a limit only on the other side. In aprotic solvents, such as benzene or chloroform, there are no limits, since the solvent merely serves as a diluent, and it is only necessary to measure the concentrations of two of the four participants in the equilibrium. However, most acid-base systems are not very soluble in aprotic solvents, and ion-pairing and complexing often become troublesome.

Measurements of Solvent Acidity.[33] So far we have seen that acid or base strength depends on the acidity or basicity of the solvent, but other characteristics of the solvent are also important. One of these is the dielectric constant, and it is important because it is a measure of the ion-solvating ability of the solvent. Solvents with high dielectric constants (e.g., H_2O) completely solvate each ion. When the dielectric constant is lower, then ions aggregate, so that ion pairs and larger aggregations are present. This usually makes little difference when the equation has the same total charge on both sides, as in $HA^+ + B \rightleftharpoons HB^+ + A$, but when the total charge increases, as, for example, in $HA + B \rightleftharpoons HB^+ + A^-$, then a solvent with high dielectric constant pushes the equilibrium farther to the right than does one with a lower constant. Even when the charge is unchanged, the dielectric constant of the solvent may still make a difference if the ion (or ions) on the left are more solvated than the ones on the right. Also the solvent may cause differential solvation in another way, quite different from the effect of dielectric constant, arising from the difference in solvation of anions by a protic solvent (which can form hydrogen bonds) and an aprotic one.[34] The effect can be extreme: in dimethylformamide, picric acid is stronger than HBr.[35] This particular result can be attributed to size. That is, the large ion $(O_2N)_3C_6H_2O^-$ is better solvated by dimethylformamide than the smaller ion Br^-; while in a protic solvent like water the solvation of an anion is by the small unshielded proton.[36]

A measurement of solvent acidity is thus needed which takes into account factors such as dielectric constant and which applies to mixed solvents as well. The Hammett acidity function is a measurement which is used for acidic solvents of high dielectric constant.[37] For any solvent, including mixtures of solvents (but the proportions of the mixture must be specified), a value H_0 is defined as

$$H_0 = \mathrm{p}K_{\mathrm{AH}_w^+} + \log \frac{[\mathrm{A}]}{[\mathrm{AH}^+]}$$

H_0 is measured by using "indicators" which are weak bases and so are partly converted in these acidic solvents. Typical indicators are *o*-nitroanilinium ion, with a pK in water of -0.29, and 2,4-dinitroanilinium ion, with a pK in water of -4.53. For a given solvent, $[\mathrm{A}]/[\mathrm{AH}^+]$ is measured for one indicator, usually by spectrophotometric means. Then, using the known pK in water for that indicator, H_0 may be calculated for that solvent system. In practice, several indicators are used, so that an average H_0 is taken. Once H_0 is known for a given solvent system, pK_a values in it may be calculated for any other acid-base pair.

---

[33] For fuller treatments, see Ref. 6, pp. 485–499; Deno, *Surv. Progr. Chem.* **2**, 155–187 (1964), pp. 169–178; and Arnett, *Progr. Phys. Org. Chem.* **1**, 223–403 (1963), pp. 233–258.

[34] For a review, see Parker, *Quart. Rev. (London)* **16**, 163–187 (1962).

[35] Sears, Wolford, and Dawson, *J. Electrochem. Soc.* **103**, 633 (1956).

[36] Miller and Parker, *J. Am. Chem. Soc.* **83**, 117 (1961).

[37] For reviews of acidity functions, see Ref. 33; Paul and Long, *Chem. Rev.* **57**, 1–45 (1957); Long and Paul, *Chem. Rev.* **57**, 935–1010 (1957); and Bowden, *Chem. Rev.* **66**, 119–131 (1966).

H_0 is defined only for neutral bases, whose conjugate acids therefore have a charge of $+1$. An analogous function for bases with a charge of -1 is called H_-, but results with this function are less consistent than with H_0. The symbol h_0 is defined as

$$h_0 = \frac{a_{\mathrm{H}^+} f_{\mathrm{I}}}{f_{\mathrm{HI}^+}}$$

where a_{H^+} is the activity of the proton and f_{I} and f_{HI^+} are the activity coefficients of the indicator and conjugate acid of the indicator, respectively. H_0 is related by h_0 by

$$H_0 = -\log h_0$$

so that H_0 is analogous to pH, and h_0 to $[\mathrm{H}^+]$, and indeed in dilute aqueous solution H_0 and $H_- = \mathrm{pH}$.

H_0 and H_- reflect the ability of the solvent system to donate protons, but they can be applied only to acidic solutions of high dielectric constant, mostly mixtures of water with acids like nitric, sulfuric, perchloric, etc. It is apparent that the H_0 treatment is valid only when $f_{\mathrm{I}}/f_{\mathrm{HI}^+}$ is independent of the nature of the base (the indicator). Since this is so only when the bases are structurally similar, the treatment is limited. Even when similar bases are compared, many deviations are found.[38] Other acidity scales have been set up, among them H_{R} for aryl carbinols,[39] $H_{\mathrm{R'}}$ for aryl olefins and other molecules whose conjugate acids are stable carbonium ions which do not form hydrogen bonds with the solvent,[40] and H_{A} for unsubstituted amides.[41]

For a number of years it was believed that, when log k (the rate constant) for an acid-catalyzed reaction was linear with $-H_0$, then the transformation of the protonated substrate AH^+ to the transition state did not involve a molecule of water, but when log k was linear with log [HA], then a molecule of water was required. This was known as the Zucker-Hammett hypothesis.[42] However, in most cases the rates did not follow either line, and the Zucker-Hammett hypothesis has now been shown to be invalid.[43] A new classification system has been devised by Bunnett[44] for reactions occurring in moderately concentrated acid solutions. ($\log k_\psi + H_0$) is plotted against $\log a_{H_2O}$, where k_ψ is the pseudo-first-order rate constant for the protonated species, and a_{H_2O} is the activity of water. Most such plots are linear or nearly so. According to Bunnett, the slope of this plot (w) tells something about the mechanism. Where w is between -2.5 and 0, water is not involved in the rate-determining step; where w is between 1.2 and 3.3, water is a nucleophile in the rate-determining step; and a value of w between 3.3 and 7 indicates that water is a proton transfer agent. These rules hold for acids in which the proton is attached to oxygen or nitrogen.[45]

---

[38] For example, see Kresge, Barry, Charles, and Chiang, *J. Am. Chem. Soc.* **84,** 4343 (1962); Katritzky, Waring, and Yates, *Tetrahedron* **19,** 465 (1963); Arnett and Mach, *J. Am. Chem. Soc.* **86,** 2671 (1964); Jorgenson and Hartter, *J. Am. Chem. Soc.* **85,** 878 (1963). Also see the discussion in Arnett, Ref. 33, pp. 236–242.

[39] Deno, Jaruzelski, and Schriesheim, *J. Am. Chem. Soc.* **77,** 3044 (1955); Deno, Berkheimer, Evans, and Peterson, *J. Am. Chem. Soc.* **81,** 2344 (1959).

[40] Deno, Groves, and Saines, *J. Am. Chem. Soc.* **81,** 5790 (1959); Deno, Groves, Jaruzelski, and Lugasch, *J. Am. Chem. Soc.* **82,** 4719 (1960).

[41] Yates, Stevens, and Katritzky, *Can. J. Chem.* **42,** 1957 (1964); Yates and Riordan, *Can. J. Chem.* **43,** 2328 (1965).

[42] Zucker and Hammett, *J. Am. Chem. Soc.* **61,** 2791 (1939).

Acid and Base Catalysis.[46] The old idea that a catalyst is something which merely increases the rate of a reaction which would proceed without the catalyst, only more slowly, has been found to be invalid for most reactions which are acid- or base-catalyzed. In these cases there is no reaction at all without at least some catalyst. Older workers were deceived because often only a trace of catalyst is necessary. The catalyst is involved in a fundamental way in the mechanism. Nearly always the first step of such a reaction is a proton transfer between the catalyst and the substrate.

Reactions may be catalyzed by acid or base in two different ways, called *general* and *specific catalysis*. If the rate of an acid-catalyzed reaction run in a solvent S is proportional to [SH$^+$], then the reaction is said to be subject to *specific acid catalysis,* the acid being SH$^+$. The acid which is put into the solvent may be stronger or weaker than SH$^+$, but the rate is proportional only to the [SH$^+$] that is actually present in the solution (derived from $S + HA \rightleftharpoons SH^+ + A^-$) and the identity of HA makes no difference except insofar as it determines the position of equilibrium and hence the [SH$^+$]. Most measurements have been made in water, where SH$^+$ is H_3O^+.

In *general acid catalysis,* the rate is increased not only by an increase in [SH$^+$] but also by an increase in the concentration of other acids (for example, in water by phenols or carboxylic acids). These other acids increase the rate even when [SH$^+$] is held constant. In this type of catalysis the strongest acids catalyze best, so that, in the example given, an increase in the phenol concentration would catalyze the reaction much less than a similar increase in [H_3O^+]. This relationship between acid strength of the catalyst and its catalytic ability may be expressed by the *Brönsted catalysis equation:*

$$\log k = \alpha \log K_a + C$$

where k is the rate constant for a reaction catalyzed by an acid of ionization constant K_a. According to this equation, when $\log k$ is plotted against $\log K_a$ for catalysis of a given reaction by a series of acids, a straight line should be obtained with slope α and intercept C. Although straight lines are obtained in many cases, this is not always the case. The relationship usually fails when acids of different types are being compared. For example, it is much more likely to hold for a group of substituted phenols than for a collection of acids which contains both phenols and carboxylic acids. The Brönsted equation is a *linear free-energy relationship* (see p. 240).

---

[43] Koskikallio and Whalley, *Trans. Faraday Soc.* **55**, 815 (1959), *Can. J. Chem.* **37**, 788 (1959).

[44] Bunnett, *J. Am. Chem. Soc.* **83**, 4956, 4968, 4973, 4978 (1961).

[45] The Bunnett w treatment has been criticized by Long and Bakule, *J. Am. Chem. Soc.* **85**, 2313 (1963).

[46] For a full discussion, see Bell, Ref. 1, pp. 124–182.

Analogously, there are *general* and *specific* (S^- from an acidic solvent SH) *base-catalyzed reactions*. The Brönsted law for bases is

$$\log k = \beta \log K_b + C$$

A knowledge of whether a reaction is subject to general or specific acid catalysis supplies information about the mechanism. For any acid-catalyzed reaction we may write

$$\mathbf{A} \xrightleftharpoons{\mathbf{SH^+}} \mathbf{AH^+} \qquad (1)$$

$$\mathbf{AH^+} \longrightarrow \text{products} \qquad (2)$$

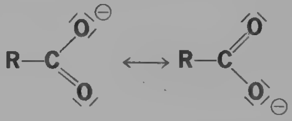
If the reaction is catalyzed only by the specific acid SH^+, it means that step (1) is rapid and step (2) is rate-controlling, since an equilibrium has been rapidly established between A and the strongest acid present in the solution, namely, SH^+ (since this is the strongest acid which can be present in S). On the other hand, if step (2) is faster, then there is no time to establish equilibrium, and the rate-determining step must be step (1). This step will be affected by all the acids present, and the rate will reflect the sum of the effects of each acid (general acid catalysis). General acid catalysis is also observed if the slow step is reaction of a hydrogen-bond complex A $\cdots\cdots$ HB, since each complex will react with a base at a different rate. A comparable discussion may be used for general and specific base catalysis. Further information may be obtained from the values α and β in the Brönsted catalysis equations, since these are approximate measures of the extent of proton transfer in the transition state.

Lewis Acids and Bases. At about the same time that Brönsted proposed his acid-base theory, Lewis put forth a broader one. A base in the Lewis theory is the same as in the Brönsted one, namely, a compound with an available pair of electrons, either unshared or in a π orbital. A *Lewis acid,* however, is any species which has a vacant orbital which it can use to form a covalent bond with the electron pair of the base. In the Brönsted picture, the acid is a proton donor, but in the Lewis picture the proton itself is the acid since it has a vacant orbital. A Brönsted acid becomes, in the Lewis picture, the compound that gives up the actual acid. The advantage of the Lewis theory is that it correlates the behavior of many more processes. For example, $AlCl_3$ and BF_3 are Lewis acids because they have only six electrons in the outer shell and have room for eight. $SnCl_4$ and SO_3 have eight, but their central elements, not being in the first row of the periodic table, have room for ten or twelve. Other Lewis acids are simple cations, like Ag^+. All reactions in which a covalent bond is formed through one species contributing a filled and the other a vacant orbital may be regarded as Lewis acid-base reactions.

The Effects of Structure and Medium on the Strengths of Acids and Bases.[47] Effects of structure on acidity may be divided into several classifications, though in many cases it is not possible to say just how much contribution is made by a given effect.

1. *Inductive effects.* These have already been discussed (p. 19). In general, electron-donating groups reduce acidity and increase basicity, and electron-withdrawing groups act oppositely. However, many apparent anomalies are known. For example, water is a stronger base than methanol or ethanol; solvation effects (p. 229) may be responsible in this case.

2. *Resonance effects.* Resonance which stabilizes an acid, but not its conjugate base, results in the acid's having a lower acidity than otherwise expected, and vice versa. For example, primary alcohols are much weaker acids than the corresponding carboxylic acids, because the conjugate base of RCH_2OH (that is, RCH_2O^-) is not stabilized by resonance, but the conjugate base of RCOOH is so stabilized:



Similarly, aromatic amines, which are stabilized by resonance (p. 36), are much weaker bases than aliphatic amines, where the electron density of the unshared pair lies entirely on the nitrogen atom.

3. *Statistical effects.* In a symmetrical dibasic acid, the first dissociation constant is twice as large as expected, since there are two equivalent ionizable hydrogens, while the second constant is only one-half as large as expected because the conjugate base can pick up a proton at two equivalent sites. So K_1/K_2 should be 4, and approximately this value is found for dicarboxylic acids where the two groups are sufficiently far apart in the molecule that they do not influence each other. A similar argument holds for molecules with two equivalent basic groups.

4. *Hydrogen bonding.* Internal hydrogen bonding can greatly influence acid or base strength. For example, the pK for *o*-hydroxybenzoic acid is 2.98, while the value for the para isomer is 4.58. Internal hydrogen bonding between the OH and COO^- groups of the conjugate base of the ortho isomer stabilizes it and results in an increased acidity.

5. *Steric effects.*[48] The proton itself is so small that direct steric hindrance is seldom encountered in proton transfers, although 2,6-di-*tert*-butylpyridine has a pK about 1 to 2 units lower than other 2,6-dialkylpyridines.[49] Steric

---

[47] For reviews, see Ref. 21 and Ref. 46, pp. 87–108. For discussions of the strengths of organic bases and acids, see, respectively, Clark and Perrin, *Quart. Rev.* (*London*) **18**, 295–320 (1964); and Barlin and Perrin, *Quart. Rev.* (*London*) **20**, 75–101 (1966).

[48] For a review, see Gold, *Progr. Stereochem.* **3**, 169–201 (1962).

[49] Brown and Kanner, *J. Am. Chem. Soc.* **88**, 986 (1966).

effects are much more common in Lewis acid-base reactions in which larger acids are used. Spectacular changes in the order of base strength have been demonstrated when the size of the acid was changed. Table 2 shows the order of base strength of simple amines when compared against acids of various size.[50] It may be seen that the usual order of basicity of amines (when the proton is the reference acid) may be completely inverted by using a large enough acid. The strain caused by formation of a covalent bond when the two atoms involved each have three large groups is called *face strain* or *F-strain.* When the reference acids were boranes, the order of basicity was determined by measurements of dissociation pressures.

Steric effects may indirectly affect acidity or basicity by affecting the resonance (see p. 36). For example, *o-tert*-butylbenzoic acid is about ten times as strong as the para isomer, because the carboxyl group is forced out of the plane by the *tert*-butyl group. Indeed, virtually all *o*-benzoic acids are stronger than the corresponding para isomers, regardless of whether the group on the ring is electron-donating or -withdrawing.

6. *Hybridization.* The unshared pair of a base is stabilized by increasing *s* character of its orbital. Thus $HC{\equiv}C^-$, which has more *s* character in its unshared pair than $CH_2{=}CH^-$ or $CH_3CH_2^-$ (*sp* versus sp^2 versus sp^3, respectively), is a much weaker base. This explains the relatively high acidity of acetylenes and of HCN.

Structural features are not the only factors which affect acidity or basicity. The same compound may have its acidity or basicity changed when the conditions are changed. The effects of temperature (p. 218) and some effects of solvent (p. 224) have already been discussed. Another way in which the solvent may influence acid and base strength is by differential solvation. If a base is more solvated than its conjugate acid, then this increases its stability relative to the conjugate acid. For example, Table 2 shows that, toward the proton, where steric effects are absent, methylamine is a stronger base than ammonia, and dimethylamine stronger still, results which are easily explainable on the basis of the electron-donating methyl groups. However, trimethylamine, which should be even stronger, is a weaker base than di-

TABLE 2. Bases listed in increasing order of base strength when compared with certain reference acids[50]

Reference acid *Increasing order of base strength*	H^+ *or* BMe_3	BMe_3	$B(CMe_3)_3$	
↓	NH_3 Me_3N $MeNH_2$ Me_2NH	Et_3H NH_3 Et_2NH $EtNH_2$	Me_3N Me_2NH NH_3 $MeNH_2$	Et_3N Et_2NH $EtNH_2$ NH_3

---

[50] Brown, *J. Am. Chem. Soc.* **67**, 378, 1452 (1945).

methylamine or methylamine. This apparently anomalous behavior may be explained by differential hydration.[51] Thus, NH_4^+ is much better hydrated (by hydrogen bonding to the water solvent) than NH_3, because of its positive charge. It has been estimated that this effect contributes about 11 pK units to the base strength of ammonia.[52] When methyl groups replace hydrogen, this difference in hydration decreases until, for trimethylamine, it contributes only about 6 pK units to the base strength.[52] Thus the two effects act in opposite directions, the inductive effect increasing the basicity as the number of methyl groups increases, and the hydration effect decreasing it. When the effects are added, the strongest base is dimethylamine, and the weakest is ammonia.

The solvent may affect acidity or basicity even when it is aprotic. For example, the order of base strength against 2,4-dinitrophenol was $Bu_3N > Bu_2NH > BuNH_2$ in chlorobenzene; $Bu_2NH > Bu_3N > BuNH_2$ in benzene; and $Bu_2NH > BuNH_2 > Bu_3N$ in dibutyl ether.[53] The ionic strength of the solvent also influences acidity or basicity, since it has an influence on activity coefficients.

---

[51] Trotman-Dickenson, *J. Chem. Soc.* **1949**, 1293; Pearson, *J. Am. Chem. Soc.* **70**, 204 (1948); Pearson and Williams, *J. Am. Chem. Soc.* **76**, 258 (1954); Hall, *J. Am. Chem. Soc.* **79**, 5441 (1957).

[52] Condon, *J. Am. Chem. Soc.* **87**, 4481, 4485 (1965).

[53] Bayles and Taylor, *J. Chem. Soc.* **1961**, 417.

CHAPTER NINE

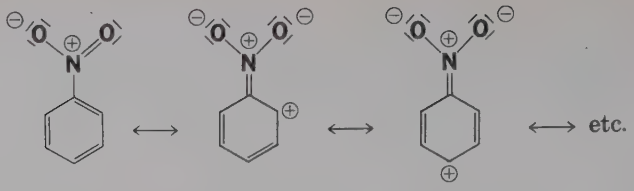
Effects of Structure on Reactivity

It is customary in writing the equation for a reaction of, say, carboxylic acids, to use the formula RCOOH, implying that all carboxylic acids undergo the reaction. Since most compounds with a given functional group do give more or less the same reactions, the custom is useful, and the practice will be used in this book. It enables a large number of individual reactions to be classified together and serves as an aid both to the memorization and the understanding of them. Organic chemistry would be a huge morass of facts without the symbol R. Nevertheless, it must be borne in mind that a given functional group does not always react the same way no matter what molecule it is a part of. The reaction at the functional group is influenced by the rest of the molecule. This influence may be so great as to stop the reaction completely, or to make it take an entirely unexpected course. Even when two compounds with the same functional group undergo the same reaction, the rates and/or the positions of equilibrium are usually different, sometimes slightly, sometimes greatly, depending on the structures of the compounds. The greatest variations may be expected when functional groups are present in addition to the one reacting.

The effects of structure on reactivity may be divided into three major types: inductive, resonance (or mesomeric), and steric. In most cases two or all three of these are operating, and it is usually not easy to tell how much of the rate enhancement (or decrease) is caused by each of the three effects.

Inductive and Resonance Effects. It is often particularly difficult to separate these two, and they are frequently grouped together under the heading of *electrical effects.* Inductive effects were discussed on pages 19–21. Table 4 in Chapter 1 (p. 21) contains a list of some $+I$ and some $-I$ groups. As for resonance effects, on page 35 it was shown how the electron-density distribution in aniline is not the same as it would be if there were no resonance interaction between the ring and the NH_2 group. Most groups which contain an unshared pair on an atom connected to an unsaturated system display a similar effect: that is, the electron density on the group is less than expected, and the density on the unsaturated system is greater. Such groups are said to be electron-donating by the resonance effect ($+M$ groups). Alkyl groups, which do not have an unshared pair, are also $+M$ groups, presumably because of hyperconjugation.

On the other hand, groups which have a multiple-bonded electronegative atom directly connected to an unsaturated system are $-M$ groups. In such cases we can draw resonance forms in which electrons have been taken from the unsaturated system into the group, for example:



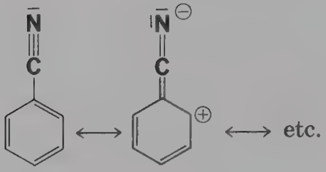


Table 1 contains a list of some $+M$ and $-M$ groups.

The resonance effect of a group, whether $+M$ or $-M$, operates only when the group is directly connected to an unsaturated system, so that, for example, in explaining the effect of the CH_3O group on the reactivity of the COOH in $CH_3OCH_2CH_2COOH$, only the inductive effect of the CH_3O needs to be considered. This is one way of separating the two effects. In *p*-methoxybenzoic acid both effects must be considered. The inductive effect operates through space, solvent molecules, or the σ bonds of a system, while the resonance effect operates through π electrons.

It must be emphasized once again that neither by the resonance nor by the inductive effect are any electrons actually being donated or withdrawn, though these terms are convenient to use (and we shall use them). As a result of both effects the electron-density distribution is not the same as it would be without the effect (see pp. 20 and 36).

One thing which complicates the study of these effects is that a given group may have an effect in the transition state which is considerably more or less than it has in the unreacting molecule. For example, consider a mole-

TABLE 1. Some groups with $+M$ and $-M$ effects, not listed in order of strength of effect

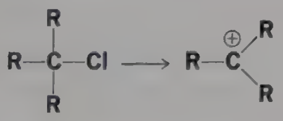
NO and Ar appear in both lists because these groups are capable of both kinds of effect

$+M$ *groups*		$-M$ *groups*	
O^-	SR	NO_2	CHO
S^-	SH	CN	COR
NR_2	Br	COOH	SO_2R
NHR	I	COOR	SO_2OR
NH_2	Cl	$CONH_2$	NO
NHCOR	F	CONHR	Ar
OR	R	$CONR_2$	
OH	NO		
OCOR	Ar		

cule $C_6H_5CH_2Y$, where Y is the reaction site. The replacement of, say, a para hydrogen by a group X gives $XC_6H_4CH_2Y$, in which the electron density at the CH_2 group is greater or less, depending on the inductive and resonance effects of X. However, when the molecule undergoes reaction, then the bond between CH_2 and Y begins to break, causing the CH_2 to have partial carbanion, carbonium-ion, or free-radical character, depending on the nature of the reaction. The group X, which in the unreacting molecule may have donated only slightly, may now donate electron density a good deal more or a good deal less. A given group X may even be electron-donating in one reaction and electron-withdrawing in another.

Steric Effects.[1] It occasionally happens that a reaction proceeds much faster or much slower than expected on the basis of electrical effects alone. Very often in these cases it may be shown that steric effects are influencing the rate. For example, Table 2 lists relative rates for the S_N2 ethanolysis of certain alkyl halides (see p. 251).[1] All of these compounds are primary bromides; the branching is on the second carbon, so that inductive-effect differences should be small. As Table 2 shows, the rate decreases with increasing β branching, and reaches a very low value for neopentyl bromide. This reaction is known to involve an attack by the nucleophile from a position opposite to that of the bromine (see p. 252). The great decrease in rate may be attributed to "steric hindrance," a sheer physical blockage to the attack of the nucleophile. Another example of steric hindrance is found in 2,6-disubstituted benzoic acids, which are difficult to esterify no matter what the inductive or resonance effects of the groups in the 2- or the 6-position.

Not all steric effects decrease reaction rates. In the hydrolysis of RCl by an S_N1 mechanism (see p. 256), the first step, which is rate-determining, involves ionization of the alkyl chloride to a carbonium ion:



The central carbon in the alkyl chloride is sp^3 hybridized and thus has angles of about 109.5°, but when it is converted to the carbonium ion,

---

[1] For a review, see Hughes, *Quart. Rev. (London)* **2**, 107–131 (1948).

TABLE 2. Relative rates of reaction of RBr with ethanol[1]

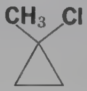
R	*Relative rate*
CH_3	17.6
CH_3CH_2	1
$CH_3CH_2CH_2$	0.28
$(CH_3)_2CHCH_2$	0.030
$(CH_3)_3CCH_2$	4.2×10^{-6}

TABLE 3. Rates of hydrolysis of tertiary alkyl chlorides at 25° in 80% aqueous ethanol[2]

Halide	*Rate*
Me_3CCl	0.033
Me_2EtCCl	0.055
$MeEt_2CCl$	0.086
Et_3CCl	0.099
Me_2(*iso*-Pr)CCl	0.029
Me(*iso*-Pr)$_2$CCl	0.45

the hybridization becomes sp^2 and the preferred angle is 120°. If the halide is tertiary and the three alkyl groups are large enough, they will be pushed together by the enforced tetrahedral angle, resulting in strain (see p. 122). This type of strain is called *B-strain* (for back strain), and it can be relieved by ionization to the carbonium ion. The rate of ionization (and hence the solvolysis rate) of a molecule in which there is B-strain would therefore be expected to be larger than in cases where B-strain is not present. Table 3 shows that this is so.[2] Substitution of ethyl groups for the methyl groups of *tert*-butyl chloride does not cause B-strain; the increase in rate is relatively small and the rate smoothly rises with the increasing number of ethyl groups. The rise is caused by normal inductive and resonance (hyperconjugation) effects. Substitution by one isopropyl group is not greatly different. But with the second isopropyl group the crowding is now great enough to cause B-strain, and the rate is increased tenfold. Substitution of a third isopropyl group increases the rate still more.

Another type of strain which can affect rates is called *I-strain* (internal strain).[3] This type of strain occurs in small-ring compounds such as



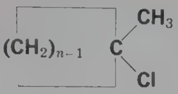
In a normal S_N1 process, the central carbon goes from a tetrahedral angle of about 109.5° to a trigonal angle of 120°, but in the alicyclic compound shown, the angle cannot change much unless the ring opens up. This means that the normal strain present where a carbon has a bond angle of 60° but would like to have 109.5° is made even greater in the intermediate, since the carbon still has a bond angle of 60°, but now would like to have an angle of 120°. This means that the energy of the transition state is higher than it would be if this strain were absent, and consequently the activation energy of the reaction is raised. Cyclopropyl halides should thus undergo S_N1 reactions more slowly than larger rings. This type of strain should also be present, though much less severe, in four-membered rings. Table 4 shows that a four-membered ring compound reacted much more slowly than the open-

---

[2] Brown and Fletcher, *J. Am. Chem. Soc.* **71,** 1845 (1949).

[3] For a review, see Gol'dfarb and Belen'kii, *Russ. Chem. Rev.* **29,** 214–235 (1960), pp. 221–228.

TABLE 4. Relative rates of solvolysis of



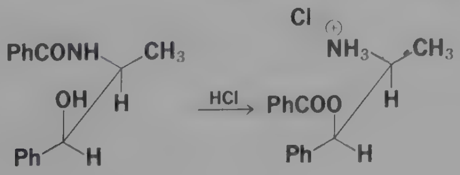
in 80% ethanol at 25°[5]

n	*Relative rate*	n	*Relative rate*
4	0.074	10	6.23
5	43.7	11	4.20
6	0.35	13	1.00
7	38.1	15	0.64
8	100	For reference:	
9	15.4	*tert*-BuCl 1.0	

chain *tert*-butyl chloride, as predicted by the concept of I-strain. The corresponding three-membered compound could not be prepared, but presumably it would have reacted more slowly still. Cyclopropyl tosylate does react about 10^6 times more slowly than cyclobutyl tosylate in acetic acid at 60°.[4]

In five-membered rings, and in rings of seven or more, the chief source of strain is nonbonded interactions (see p. 119). Change from a tetrahedral to a trigonal carbon in these compounds should relieve such strain. Table 4 bears this out.[5] However, the abnormally slow rates of cyclopropyl systems are not caused entirely by I-strain. It has been pointed out that the σ bonds of cyclopropane rings have considerable π character (p. 117), so that we should expect cyclopropyl halides to resemble vinyl halides in reactivity. As shown on page 282, vinyl halides are very unreactive to S_N1 substitutions.

Conformational effects on reactivity may be considered under the heading of steric effects, although in these cases we are considering not the effect of a group X and that of another group X′ upon reactivity at a site Y, but the effect of the conformation of the molecule. Many reactions fail entirely unless the molecules are able to assume the proper conformation. An example is the rearrangement of N-benzoylnorephedrine. The two diastereomers of this compound behave very differently when treated with alcoholic HCl. In one of the isomers N⟶O migration takes place, while the other does not react at all.[6] In order for the migration to take place, the nitrogen must be near the oxygen (gauche to it). When **1** assumes this conformation, the



1

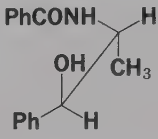
---

[4] Roberts and Chambers, *J. Am. Chem. Soc.* **73**, 5034 (1951).

[5] Brown and Borkowski, *J. Am. Chem. Soc.* **74**, 1894 (1952).

[6] Fodor, Bruckner, Kiss, and Óhegyi, *J. Org. Chem.* **14**, 337 (1949).

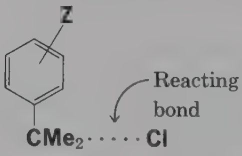
methyl and phenyl groups are trans to each other, which is a favorable position, but when **2** has the nitrogen gauche to the oxygen, the methyl must be gauche to the phenyl, which is so unfavorable that the reaction does not occur. Other examples are electrophilic additions to C=C double bonds (see p. 563) and E2 elimination reactions (see p. 728). Also, many examples are known where axial and equatorial groups behave differently.[7]



2

The Reacting-bond Rule and the Solvation Rule. Electron-donating and electron-withdrawing groups affect the transition state of a reaction. Swain and Thornton have supplied a rule, called the *reacting-bond rule,* which helps in predicting the change in transition-state geometry caused by the presence, in a reacting molecule, of a functional group located away from the reaction center.[8] To apply the rule, it is necessary to locate all the *reacting bonds* in the transition state. A reacting bond is defined as one which is present in the transition state, but entirely absent in either the reactant (for bonds being made) or the products (for bonds being broken). The reacting-bond rule predicts that, for an electron-donating substituent, the nearest reacting bond will be longer and the next nearest reacting bond shorter, in the transition state, compared to the same transition state without the functional group. An electron-withdrawing substituent shortens the nearest and lengthens the next nearest reacting bond. For reacting bonds which are more remote, the alternating effect continues.

An example of the reacting-bond rule may be found in solvolysis of cumyl chlorides. There is only one reacting bond in this S_N1 reaction (see p. 256):



Transition state

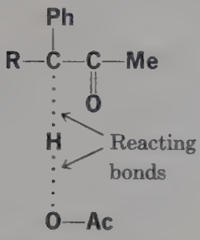
Therefore, electron-donating Z should lengthen the C—Cl bond in the transition state, and electron-withdrawing Z should shorten it. Experimentally, the reaction has been found to be more sensitive to solvent polarity for the electron-donating *m*-Me and *p*-Ph groups than for the electron-withdrawing *m*- or *p*-Cl, *p*-MeO_2C, or *p*-F_3C groups,[9] indicating that, indeed, there is more complete ionization in the transition state when electron-donating substituents are present. Thus, in this case, electron-donating groups cause the transition state to resemble more closely the intermediate carbonium ion rather than the reactants, when compared to the unsubstituted compounds. Another example is found in the enolization of 5-methyl-3-phenyl-2-hexanone, catalyzed by acetic acid or acetate ion (reaction **2-3**, p. 457):

---

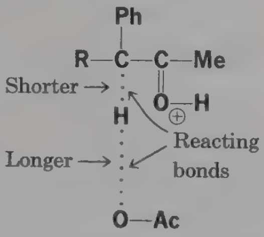
[7] For a discussion, see Eliel, "Stereochemistry of Carbon Compounds," pp. 219–234, McGraw-Hill Book Company, New York, 1962.

[8] Swain and Thornton, *J. Am. Chem. Soc.* **84**, 817 (1962). For a discussion, see Thornton, "Solvolysis Mechanisms," pp. 77–84, The Ronald Press Company, New York, 1964.

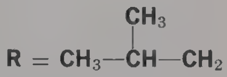
[9] Okamoto, Inukai, and Brown, *J. Am. Chem. Soc.* **80**, 4972 (1958).



Transition state for
OAc⁻ catalysis



Transition state for
HOAc catalysis



$R = CH_3-\overset{CH_3}{\overset{|}{C}H}-CH_2$

The rule predicts that the C—H bond should be shorter for acetic acid catalysis, since hydrogen is electron-withdrawing compared to no group at all. Experimentally, this should cause a larger isotope effect for acetic acid catalysis. Tritium isotope effects (see p. 215) for acetic acid and acetate catalysis were, respectively, 11.4 and 10.2.[10]

The reacting-bond rule may be rationalized on the basis of orbital overlap in the transition state. Since reacting bonds are much longer than ordinary covalent bonds, they may be regarded as electron-deficient bonds. Thus, an electron-donating group strengthens them by supplying electrons, so that the bonds can be stretched to a greater extent before the transition state is reached, hence becoming longer. This reasoning explains why the nearest reacting bond is lengthened by electron-donating groups, but it does not explain why the next nearest bond is shortened; indeed if this were the only effect, we should expect the second-nearest bond to be lengthened also, though to a lesser extent than the nearest. The second-nearest bond is shortened because of another, greater effect: the longer nearest reacting bond polarizes the electrons in the second-nearest bond, hence shortening it.

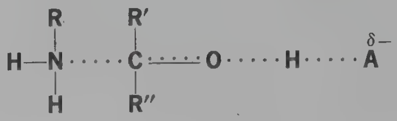
The *solvation rule* predicts the effect of substituents on the position of protons being transferred between oxygen or nitrogen atoms.[11] It states that "a proton being transferred in an organic reaction from one oxygen or nitrogen to another should lie in an entirely stable potential at the transition state and not form reacting bonds or give rise to primary hydrogen isotope effects. It should lie closer to the more basic atom (oxygen or nitrogen) at the transition state, but increasingly remote as substituents are changed to make this atom less basic."[12] An example of the use of the rule may be found in an investigation of the mechanism of the general-acid-catalyzed formation of Schiff bases, oximes, and semicarbazones (reactions **6-15**, **6-22**, and **6-21,** respectively). Two possible transition states are

---

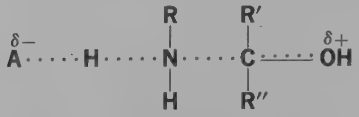
[10] Swain, Stivers, Reuwer, and Schaad, *J. Am. Chem. Soc.* **80**, 5885 (1958).

[11] Swain, Kuhn, and Schowen, *J. Am. Chem. Soc.* **87**, 1553 (1965).

[12] Swain and Worosz, *Tetrahedron Letters* **1965**, 3199.



$$\mathrm{H{-}\overset{R}{\underset{H}{N}}\cdots\cdots\overset{R'}{\underset{R''}{C}}\overset{\cdots\cdots}{-\!-\!-}O\cdots\cdots H\cdots\cdots\overset{\delta-}{A}} \qquad (1)$$



$$\mathrm{\overset{\delta-}{A}\cdots\cdots H\cdots\cdots\overset{R}{\underset{H}{N}}\cdots\cdots\overset{R'}{\underset{R''}{C}}\overset{\cdots\cdots}{-\!-\!-}\overset{\delta+}{OH}} \qquad (2)$$

If mechanism (1) is operating, then the reacting-bond rule predicts that, as R becomes electron-donating, the N—C bond will become longer and the C—O bond shorter. As the C—O bond distance decreases, the oxygen becomes less basic, so that by a combination of the two rules, we would predict that, as R becomes more electron-donating, the proton should be closer to A^- in the transition state. Fortunately, there is a way to investigate the change in the position of the proton. The slope (α) of the Brönsted equation (p. 226) falls as the length of the A—H bond in the transition state decreases. Therefore, if mechanism (1) is correct, α should fall as R becomes more electron-donating. On the other hand, if mechanism (2) is operating, we do not need the reacting-bond rule. Increasing electron-donating ability of R makes N more basic, causing (by the solvation rule) the proton to be closer to N in the transition state. Since the proton is now farther away from A, α should rise as R becomes more electron-donating. In the case of the reaction of aldehydes with semicarbazide, aniline, and hydroxylamine, α was found to fall with increasing electron donation from R, thus supporting mechanism (1).[13]

Quantitative Treatments of the Effect of Structure on Reactivity.[14] Suppose that the substitution of a group X for H in a reaction of $XCH{=}CHCH_2Y$ (the reaction taking place at the Y group) results in a rate increase by a factor of, say, 10. We would like to be able to know just what part of the increase is due to each of the effects previously mentioned. The obvious way to approach such a problem is to try to find compounds in which one or two of the factors are absent, or at least negligible. This is not easy to do acceptably, because factors which seem negligible to one investigator do not always appear so to another. The first attempt to give numerical values was that of Hammett.[15] For the cases of *m*- and *p*-XC_6H_4Y, Hammett set up the following equation:

---

[13] This analysis is from Swain and Worosz, Ref. 12. The experimental results are quoted from Jencks, *J. Am. Chem. Soc.* **81,** 475 (1959); and Cordes and Jencks, *J. Am. Chem. Soc.* **84,** 832, 4319 (1962).

[14] For reviews, see Wells, *Chem. Rev.* **63,** 171–218 (1963); Ritchie and Sager, *Progr. Phys. Org. Chem.* **2,** 323–400 (1964); Taft, in Newman, "Steric Effects in Organic Chemistry," pp. 556–675, John Wiley & Sons, Inc., New York, 1956; Taft, *J. Phys. Chem.* **64,** 1805–1815 (1960); and Pal'm, *Russ. Chem. Rev.* **30,** 471–498 (1961). For a theoretical discussion, see Ehrenson, *Progr. Phys. Org. Chem.* **2,** 195–251 (1964).

$$\log \frac{k}{k_0} = \sigma\rho$$

where k_0 is the rate constant or equilibrium constant for X = H, k is the constant for the group X, ρ is a constant for a given reaction under a given set of conditions, and σ is a constant characteristic of the group X. The equation is called the *Hammett equation.*

The value of ρ was originally set at 1.00 for dissociation of XC_6H_4COOH at 25°, and σ_m and σ_p values were then calculated for each group (for a group X, σ is different for the meta and para positions). Once a set of σ values was so obtained, ρ values could be obtained for other reactions from the rates of just two X-substituted compounds, if the σ values of the X groups were known (in practice, at least four well-spaced values are used to calculate ρ because of experimental error and because the treatment is not exact). With the ρ value thus calculated, and the known σ values for other groups, rates may be predicted for reactions which have not yet been run.

The σ values are numbers which sum up the total electrical effects (resonance plus inductive) of a group X when attached to a benzene ring. The treatment usually fails for the ortho position precisely because steric effects enter here.[16] The treatment is successful for ortho compounds when the group Y is separated from the ring so that steric effects are minimized; for example, it correlates ionization constants of *o*-$XC_6H_4OCH_2COOH$.[17]

The Hammett treatment has been applied to many reactions and to many functional groups and correlates quite well an enormous amount of data. In a review article by Jaffé[15] are listed ρ values for 204 reactions,[18] many of them having different ρ values for different conditions. Among them are reactions as disparate as the following:

Rate constants for

$ArCOOMe + OH^- \longrightarrow ArCOO^-$

$ArCH_2OCOMe + OH^- \longrightarrow ArCH_2OH$

$ArCH_2Cl + I^- \longrightarrow ArCH_2I$

$ArNH_2 + PhCOCl \longrightarrow ArNHCOPh$

$ArH + NO_2^+ \longrightarrow ArNO_2$

$ArCO_2OCMe_3 \longrightarrow$ decomposition (a free-radical process)

Equilibrium constants for

$ArCOOH + H_2O \rightleftharpoons ArCOO^- + H_3O^+$

$ArCHO + HCN \rightleftharpoons ArCH(CN)OH$

---

[15] For a review, see Jaffé, *Chem. Rev.* **53,** 191 (1953).

[16] See, for example, Watkinson, Watson, and Yates, *J. Chem. Soc.* **1963,** 5437.

[17] Charton, *Can. J. Chem.* **38,** 2493 (1960).

[18] Additional ρ values are given in Wells, Ref. 14; and in van Bekkum, Verkade, and Wepster, *Rec. trav. chim.* **78,** 821–827 (1959).

The Hammett equation has also been shown to apply to many physical measurements, including infrared frequencies and nuclear-magnetic-resonance chemical shifts. The treatment is reasonably successful whether the substrates are attacked by electrophilic, nucleophilic, or free-radical reagents, the important thing being that the mechanism be constant *within* a given reaction series.

However, there are many reactions which do not fit the treatment. These are mostly reactions where the attack is directly on the ring and where the X group is one which can enter into direct resonance interaction with the reaction site in the transition state. For these cases, two new sets of σ values have been devised: σ^+ values for cases in which an electron-withdrawing group interacts with a developing positive charge in the transition state (this includes the important case of electrophilic aromatic substitutions; see Chapter 11) and σ^- values,[19] where electron-donating groups interact with a developing negative charge. Table 5 gives σ, σ^+, and σ^- values for some common X groups.[20] As shown in the table, σ is essentially the same as σ^+ for most electron-withdrawing groups.

A positive value of σ indicates an electron-withdrawing group, and a negative value an electron-donating group. The constant ρ measures the susceptibility of the reaction to electrical effects. Reactions with a positive ρ are helped by electron-withdrawing groups, and vice versa.

Similar calculations have been made for compounds with two groups X and X′ on one ring, where the σ values have been found to be sometimes additive and sometimes not,[21] for other ring systems such as naphthalene[22] and heterocyclic rings, and for ethylenic and acetylenic systems.[23]

The Hammett equation is a *linear free-energy relationship.* This may be demonstrated as follows, for the case of equilibrium constants (for rate constants a similar demonstration may be made, with $\Delta G^\ddagger$ instead of ΔG). For each reaction, where X is any group,

$$\Delta G = -RT \ln K$$

For the unsubstituted case,

$$\Delta G_0 = -RT \ln K_0$$

---

[19] These were formerly called σ^* values, but this designation is now used for the inductive-effect values mentioned in footnote 25.

[20] σ values are taken from van Bekkum, Verkade, and Wepster, Ref. 18, and Jaffé, Ref. 15, except for the values for N_2^+, which are from Lewis and Johnson, *J. Am. Chem. Soc.* **81**, 2070 (1959), and the σ_p value for CHO, which is from Humffray, Ryan, Warren, and Yung, *Chem. Commun.* **1965**, 610. σ^- values are also from Jaffé. σ^+ values are from Okamoto, Inukai, and Brown, *J. Am. Chem. Soc.* **80**, 4969 (1958), and Brown and Okamoto, *J. Am. Chem. Soc.* **80**, 4979 (1958). See also the extensive table in Ritchie and Sager, Ref. 14, pp. 334–337.

[21] Stone and Pearson, *J. Org. Chem.* **26**, 257 (1961).

[22] Berliner and Winikov, *J. Am. Chem. Soc.* **81**, 1630 (1959).

[23] For example, see Charton, *J. Org. Chem.* **26**, 735 (1961); **30**, 552, 557, 969, 974 (1965); Hine and Bailey, *J. Am. Chem. Soc.* **81**, 2075 (1959); and Charton and Meislich, *J. Am. Chem. Soc.* **80**, 5940 (1958).

TABLE 5. σ, σ^+, and σ^- values for some common groups[20]

Group	σ_p	σ_m	σ_p^+	σ_m^+	σ_p^-
O^-	−0.52	−0.71			
CMe_3	−0.20	−0.12	−0.26	−0.06	
OH	−0.18	0.095	−0.92		
NH_2	−0.17	−0.04	−1.3	−0.16	
NMe_2	−0.17	−0.05	−1.7		
Me	−0.13	−0.07	−0.31	−0.07	
OMe	−0.11	0.08	−0.78	0.05	
H	0	0	0	0	0
Ph	0.01	0.22	−0.18	0.11	
F	0.06	0.34	−0.07	0.35	
COO^-	0.13	0.10	−0.02	−0.03	
$CONH_2$		0.28			0.63
Cl	0.24	0.37	0.11	0.40	
Br	0.27	0.39	0.15	0.41	
I	0.30	0.35	0.14	0.36	
COOMe	0.39	0.32	0.49	0.37	0.64
COOH	0.41	0.36	0.42	0.32	0.73
CHO	0.45	0.36			1.13
$COCH_3$	0.50	0.31			0.87
CN	0.67	0.61	0.66	0.56	1.00
NH_3^+		0.63			
NO_2	0.78	0.71	0.79	0.67	1.27
NMe_3^+	0.80	0.86	0.41	0.36	
N_2^+	1.8	1.7			

The Hammett equation may be rewritten

$$\log K - \log K_0 = \sigma\rho$$

so that

$$\frac{-\Delta G}{2.3RT} + \frac{\Delta G_0}{2.3RT} = \sigma\rho$$

and

$$-\Delta G = \sigma\rho 2.3RT - \Delta G_0$$

For a given reaction under a given set of conditions, ρ, R, T, and ΔG_0 are all constant, so that σ is linear with ΔG.

The Hammett equation is not the only linear free-energy relationship. About five or six are known at this time. Some of them, like the Hammett equation, correlate structural changes in reactants, but the Grunwald-Winstein relationship (see p. 296) correlates changes in solvent, and the Brönsted relation (see p. 226) relates acidity to catalysis. The Taft equation is a structure-reactivity equation which correlates only inductive effects.

Taft, following Ingold,[24] assumed that for the hydrolysis of esters, steric and resonance effects will be the same whether the hydrolysis is catalyzed by acid or base (see the discussion of ester-hydrolysis mechanisms, reaction **0-11**, p. 309). Rate differences would therefore be caused only by the inductive effects of R and R′ in RCOOR′; and inductive effects of X could be determined by measuring the rates of acid- and base-catalyzed hydrolysis of a series XCH_2COOR', where R′ would be held constant. From these rate constants, a value σ_I could be determined by the equation

$$\sigma_I \equiv 0.181\left[\log\left(\frac{k}{k_0}\right)_{\mathrm{B}} - \log\left(\frac{k}{k_0}\right)_{\mathrm{A}}\right]$$

In this equation $(k/k_0)_{\mathrm{B}}$ is the rate constant for basic hydrolysis of XCH_2COOR' divided by the rate constant for basic hydrolysis of CH_3COOR', $(k/k_0)_{\mathrm{A}}$ is the similar rate-constant ratio for acid catalysis, and 0.181 is an arbitrary constant. σ_I is a substituent constant for a group X, substituted at a saturated carbon, which reflects only inductive effects.[25] Once a set of σ_I values was obtained, it was found that the equation

$$\log\frac{k}{k_0} = \rho_I\sigma_I$$

holds for a number of reactions, among them:[26]

$RCH_2OH \longrightarrow RCH_2O^-$
$RCH_2Br + PhS^- \longrightarrow RCH_2SPh + Br^-$
Acetone + I_2, catalyzed by RCOOH $\longrightarrow$
o-Substituted-$ArNH_2 + PhCOCl \longrightarrow ArNHCOPh$

As is the case with the Hammett equation, ρ_I is constant for a given reaction under a given set of conditions. For very large groups the relationship may fail because of the presence of steric effects, which are not constant. The equation also fails when X enters into resonance with the reaction center to different extents in the initial and final (or transition) states. A list of some σ_I values is given in Table 6. The σ_I values are about what we would expect for pure inductive-effect values (see p. 21) and are additive, as inductive effects, but not resonance or steric effects, would be expected to be. Thus, in moving a group one carbon down the chain, there is a decrease by a factor of 2.8 ± 0.5 (compare the values of R and RCH_2 in Table 6 for R = Ph and CH_3CO).

Since σ_p values represent the sum of inductive and resonance effects, Taft, Deno, and Skell proposed that these values could be divided into inductive

---

[24] Ingold, *J. Chem. Soc.* **1930**, 1032.

[25] There is another set of values (called σ^* values) which are also used to correlate inductive effects. These are related to σ_I values by

$$\sigma_{I(X)} = 0.45\sigma^*_{(XCH_2)}$$

Following the suggestion by Ritchie and Sager (Ref. 14), we discuss only σ_I and not σ^* values. See also footnote 19.

[26] Wells, Ref. 14, p. 196.

TABLE 6. σ_R **and** σ_I **values for some groups**[28]

Group	σ_R	σ_I	*Group*	σ_R	σ_I
NH_2	−0.76	0.10	CMe_3	−0.09	−0.07
OH	−0.60	0.25	$OCOCH_3$	−0.09	0.39
OMe	−0.51	0.17	H	0	0
F	−0.44	0.52	NMe_3^+	0	0.86
Cl	−0.24	0.47	CF_3	0.09	0.41
$NHCOCH_3$	−0.22	0.28	CN	0.10	0.58
Br	−0.22	0.45	COOEt	0.11	0.32
I	−0.11	0.39	$COCH_3$	0.15	0.28
Me	−0.11	−0.05	CH_2COCH_3		0.10
Ph	−0.11	0.10	NO_2	0.16	0.63
CH_2Ph		0.04			

and resonance contributions, if σ_I is taken to represent the inductive portion.[27] The resonance contribution was given the symbol σ_R and defined as

$$\sigma_R = \sigma_p - \sigma_I$$

That is, σ_I is the effect that would be observed if the only effect present were that caused by σ *electrons.* The total effect resulting from the presence of π electrons is then taken as σ_R. Some values of σ_R are given in Table 6.[28] The sum of the σ_I and σ_R values in Table 6 do not necessarily correspond to the σ_p values in Table 5 because they were not calculated from those σ_p values, but from σ_p values obtained only from the ionization of benzoic acids and the saponification of benzoic esters. σ_I values for alkyl groups show the inductive order, while σ_R values show the Baker-Nathan order (Table 7).[29] This is evidence for hyperconjugation. It may be noticed that $\sigma_R + \sigma_I$ (that is, σ_p) for each of the alkyl groups in Table 7 is −0.15.

Another way of measuring resonance effects is by use of ^{19}F nuclear magnetic resonance of *m*- and *p*-XC_6H_4F. The chemical shift of the fluorine is

TABLE 7. σ_R **and** σ_I **values for some alkyl groups**[29]

Group	σ_R	σ_I
H	0	0
Me	−0.102	−0.046
Et	−0.094	−0.055
iso-Pr	−0.086	−0.064
tert-Bu	−0.078	−0.074

---

[27] Taft, Deno, and Skell, *Ann. Rev. Phys. Chem.* **9**, 287–314 (1958), pp. 290–293.

[28] These values are from Ref. 27, except that the values for the CH_2Ph and CH_2COCH_3 groups were calculated from σ^* values by the formula given in footnote 25.

[29] Taft and Lewis, *Tetrahedron* **5**, 210 (1959).

TABLE 8. Chemical-shift differences between p-XC_6H_4F and m-XC_6H_4F[30]

Group	*Shift, parts per million*
NH_2	−13.8
OMe	−12.6
OH	−12.1
F	−9.8
$OCOCH_3$	−6.0
Cl	−5.1
H	0
CH_3CO	5.6
COOEt	5.8
NO_2	5.8
CHO	7.8

taken to be a measure of the electron density around the fluorine (see p. 193). The inductive effect is regarded as the same for the *meta* and *para* positions, so that the difference in chemical shifts should be proportional to the resonance effect of X. In Table 8 are given chemical-shift differences for various groups.[30] These have been converted, by a general formula, into σ_R values[31] which agree in general tendency, though not exactly, with those in Table 6. It has been shown[32] that electron density on fluorine cannot always be correlated with ^{19}F chemical shifts.

Taft was also able to isolate steric effects. For the acid-catalyzed hydrolysis of esters in aqueous acetone, log k/k_0 was shown to be insensitive to polar effects. In cases where resonance interaction was absent, this value was proportional only to steric effects (and any others which are not inductive or resonance). The equation is

$$\log \frac{k}{k_0} = E_s$$

The methyl group is taken as standard, with the value 0. Some E_s values are given in Table 9.[33] This treatment is more restricted than those previously discussed, since it requires more assumptions, but the E_s values are approximately in order of the size of the groups.

An equation taking into account both inductive and steric factors would be

$$\log \frac{k}{k_0} = \rho_I \sigma_I + \delta E_s$$

---

[30] Taft, Glick, Lewis, Fox, and Ehrenson, *J. Am. Chem. Soc.* **82,** 756 (1960).
[31] Taft, Price, Fox, Lewis, Anderson, and Davis, *J. Am. Chem. Soc.* **85,** 3146 (1963).
[32] Holmes and Gallagher, *Inorg. Chem.* **2,** 433 (1963).
[33] Taft in Newman, Ref. 14, p. 598.

TABLE 9. E_s values for some groups[33]

Group	E_s	*Group*	E_s
H	1.24	Cyclohexyl	−0.79
Me	0	*sec*-Bu	−1.13
Et	−0.07	F_3C	−1.16
$ClCH_2$	−0.24	*tert*-Bu	−1.54
$BrCH_2$	−0.27	Neopentyl	−1.85
Pr	−0.36	Cl_3C	−2.06
ICH_2	−0.37	Br_3C	−2.43
$PhOCH_2$	−0.38	$(Me_3CCH_2)_2CH$	−3.18
iso-Pr	−0.47	Et_3C	−3.8

where δ is analogous to ρ.[34] However, not much work has been done on this.

Linear free-energy relationships may have mechanistic implications. If $\log k/k_0$ is linear with the appropriate σ, then it is likely that the same mechanism is operating throughout the series. If not, then a smooth curve usually indicates a gradual change in mechanism, while a pair of intersecting straight lines indicates an abrupt change. Information may also be obtained from the magnitude and sign of ρ. Positive ρ values indicate that the reaction is facilitated by electron-withdrawing groups (and vice versa).

---

[34] Wells, Ref. 14, p. 199.

Part Two

In Part 2 of this book we shall be directly concerned with organic reactions and their mechanisms. The reactions have been classified into 10 chapters, based primarily on reaction type and not on mechanism. These types are substitutions, additions to multiple bonds, eliminations, rearrangements, and oxidation-reduction reactions. Five chapters have been devoted to substitutions, and these are classified on the basis of mechanism as well as substrate. Chapters 10 and 13 include nucleophilic substitutions at aliphatic and aromatic substrates, respectively. Similarly, Chapters 12 and 11 deal with electrophilic substitutions at aliphatic and aromatic substrates, respectively. All free-radical substitutions, both aromatic and aliphatic, are discussed in Chapter 14. Additions to multiple bonds are classified not according to mechanism, but according to the type of multiple bond. All additions to carbon-carbon multiple bonds are dealt with in Chapter 15, while in Chapter 16 we treat additions to other multiple bonds. One chapter is devoted to each of the three remaining reaction types: Chapter 17, eliminations; Chapter 18, rearrangements; and Chapter 19, oxidation-reduction reactions. This last chapter considers only those oxidation-reduction reactions which could not be conveniently treated in any of the other categories (except for oxidative eliminations).

Each chapter in Part 2 consists of two main sections. The first section of each chapter (except Chapter 19) deals with mechanism and reactivity. For each reaction type there are a number of possible mechanisms. These are discussed in turn, with particular attention given to the evidence for each mechanism and to the factors which cause one mechanism, rather than another, to prevail in a given reaction. Following the discussion of mechanisms, there is in each chapter a section on reactivity including, where pertinent, a consideration of orientation, and of the factors affecting it.

The second main section in each chapter is a treatment of reactions belonging to the category indicated by the title of the chapter. It is not possible—nor indeed would it be wise even if it were possible—to discuss in a book of this nature all or nearly all *known reactions. However, an attempt has been made to include all of the important reactions of standard organic chemistry which may be used to prepare relatively pure compounds in reasonable yields. In order to present a well-rounded picture and to include some reactions which are traditionally discussed in textbooks, a number of reactions which do not fit into the above category have been included. The scope of the coverage is apparent from the fact that more than 90% of the individual preparations given in* Organic Syntheses *are treated in this book. However, certain special areas have been covered only lightly, or not at all. Among these are electrochemical, photochemical, and polymerization reactions, and the preparation and reactions of heterocyclic compounds, carbohydrates, steroids, and compounds containing phosphorus, silicon, arsenic, boron, and mercury. The basic principles involved in these areas are of course no different from those in the areas more fully treated. Even with these omissions, however, some 470 reactions are treated in this book.*

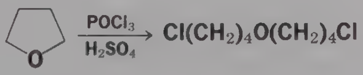
Each reaction is discussed in its own numbered section.[1] *These are numbered consecutively within a chapter. The* first *digit in each number is the* second *digit of the chapter number. Thus, reaction* **6-1** *is the first reaction of Chapter 16, and reaction* **3-21** *is the twenty-first reaction of Chapter 13. The second part of the reaction number has no other significance. The order in which the reactions are presented is not arbitrary but is based on an orderly outline which depends on the reaction type. The placement of each reaction in a separate numbered section serves as an aid to both memory and understanding, by setting clear boundary lines between one reaction and another, even if these boundary lines must be arbitrary; and by clearly showing the relationship of each reaction to all the others. Within each section, the scope and utility of the reaction are discussed, and references are given to review articles, if any. If there are features of the mechanism which especially pertain to that reaction, these*

---

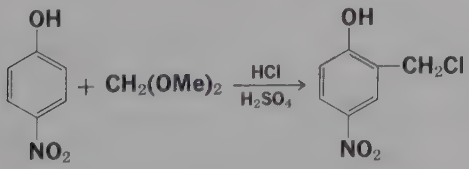
[1] The classification of reactions into sections is, of course, to some degree arbitrary. Each individual reaction (for example, $CH_3Cl + CN^- \longrightarrow CH_3CN$ and $C_2H_5Cl + CN^- \longrightarrow C_2H_5CN$) is different, and custom generally decides how we group them together. Individual preferences also play a part. Some chemists would say that $C_6H_5N_2^+ + CuCN \longrightarrow C_6H_5CN$ and $C_6H_5N_2^+ + CuCl \longrightarrow C_6H_5Cl$ are examples of the "same" reaction, and others would say that they are not, but that $C_6H_5N_2^+ + CuCl \longrightarrow C_6H_5Cl$ and $C_6H_5N_2^+ + CuBr \longrightarrow C_6H_5Br$ are examples of the "same" reaction. No claim is made that the classification system used in this book is more correct than any other.

are also discussed within the section, rather than in the first part of the chapter where the discussion of mechanism is more general.

At the end of each numbered section there is a list of Organic Syntheses *references (abbreviated OS). With the exception of a few very common reactions* (**2-3, 2-13, 2-14,** *and* **2-24**), *the list includes* all Organic Syntheses *references for each reaction. The volumes of* Organic Syntheses *which have been covered are Collective Volumes* **I** *to* **IV** *and individual volumes* **40** *to* **46.** *Where no* Organic Syntheses *references are listed at the end of a section, the reaction has not been reported in* Organic Syntheses *through volume* **46.** *Certain ground rules were followed in assembling these lists. A reaction in which two parts of a molecule are independently undergoing simultaneous reaction is listed under both reactions. Similarly, if two reactions happen (or might happen) rapidly in succession without the isolation of an intermediate, the reactions are listed in both places. For example, at OS* **IV,** *266 is*



This reaction is treated as reaction **0-65** *followed by reaction* **0-20,** *and is listed at both places. However, certain reactions are not listed because they are trivial examples. An instance of this is the reaction found at OS* **III,** *468:*



This is a chloromethylation reaction and is consequently listed at reaction **1-25.** *However, in the course of the reaction formaldehyde is generated from the acetal. This reaction is not listed at* **0-7** *(hydrolysis of acetals) because it is not really a preparation of formaldehyde. Another instance comes from OS* **III,** *841:*

$$Ph_3COH + CH_3COCl \longrightarrow Ph_3CCl + CH_3COOH$$

In this case, an acyl halide is converted to the corresponding acid (reaction **0-9***), but the reaction is not listed at* **0-9,** *because it is obviously designed to prepare triphenylmethyl chloride and not acetic acid. Thus the reaction is listed only at* **0-64.**

CHAPTER TEN

Aliphatic Nucleophilic Substitution

In a nucleophilic substitution the attacking reagent (the nucleophile) brings an electron pair to the substrate, and the leaving group comes away with an electron pair:

$$\mathrm{R}\overset{\curvearrowright}{-}\mathrm{X} + \bar{\mathrm{Y}} \longrightarrow \mathrm{R{-}Y} + \bar{\mathrm{X}}$$

This equation says nothing about charges. Y may be neutral or negatively charged; RX may be neutral or positively charged; so that there are four charge types, examples of which are

Type I $\mathrm{R{-}I} + \mathrm{OH^-} \longrightarrow \mathrm{R{-}OH} + \mathrm{I^-}$

Type II $\mathrm{R{-}I} + \mathrm{NMe_3} \longrightarrow \mathrm{R{-}\overset{\oplus}{N}Me_3} + \mathrm{I^-}$

Type III $\mathrm{R{-}\overset{\oplus}{N}Me_3} + \mathrm{OH^-} \longrightarrow \mathrm{R{-}OH} + \mathrm{NMe_3}$

Type IV $\mathrm{R{-}\overset{\oplus}{N}Me_3} + \mathrm{H_2S} \longrightarrow \mathrm{R{-}\overset{\oplus}{S}H_2} + \mathrm{NMe_3}$

In all cases, Y must have an unshared pair of electrons, so that all nucleophiles are Lewis bases. When Y is the solvent, the reaction is called solvolysis. Nucleophilic substitutions at an aromatic carbon are considered in Chapter 13.

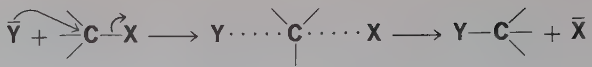
MECHANISMS

Several distinct mechanisms are possible for aliphatic nucleophilic substitution reactions, depending on the substrate, nucleophile, leaving group, and reaction conditions, but in all of them the attacking reagent carries the electron pair with it, so that the similarities are greater than the differences. Mechanisms that occur at a saturated carbon atom will be considered first.[1] By far the most common are the S_N1 and S_N2 mechanisms.

The S_N2 Mechanism. S_N2 stands for *substitution nucleophilic bimolecular.* In this mechanism the nucleophile approaches the substrate from a position 180° away from the leaving group. The reaction is a one-step process, with no intermediate. The C—Y bond is formed as the C—X bond is broken:

---

[1] For a comprehensive review, see Streitwieser, *Chem. Rev.* **56**, 571–752 (1956). This review has been reprinted, and more recent material added, in Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Company, New York, 1962. For monographs on the subject, see Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," Elsevier Publishing Company, New York, 1963; and Thornton, "Solvolysis Mechanisms," The Ronald Press Company, New York, 1964.



1

The position of the atoms and electrons at the top of the curve of free energy of activation may be represented as **1**. Of course the reaction does not stop here: this is the transition state. The group X must leave as the group Y comes in, because at no time can the carbon have more than eight electrons in its outer shell. In molecular-orbital terms, the transition state may be described as a point at which the previously unshared orbital of Y overlaps with the carbon orbital to about the same extent as does the soon-to-be unshared orbital of X. During the transition state the three nonreacting groups and the central carbon are approximately coplanar. They will be exactly coplanar if both the entering and the leaving group are the same. Otherwise, they will deviate slightly from planarity depending on whether bond making or bond breaking is more important in the transition state.

There is a large amount of evidence for the S_N2 mechanism. First we may consider the kinetic evidence. Since both the nucleophile and the substrate are involved in the rate-determining step (the only step, in this case), the reaction should be first order in each component, second order overall, and should satisfy the rate expression

$$\text{Rate} = k[\text{RX}][\text{Y}] \tag{1}$$

This rate law has been found to apply in many cases. It has been noted that the 2 in S_N2 stands for bimolecular. It must be remembered that this is not always the same as second order (see p. 211). If a large excess of nucleophile is present—for example, if it is the solvent—the mechanism may still be bimolecular, though the experimentally determined kinetics will be first order:

$$\text{Rate} = k[\text{RX}] \tag{2}$$

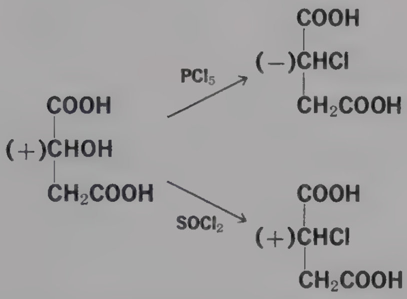
As previously mentioned (p. 211), such kinetics are called *pseudo first order*.

The kinetic evidence is a necessary but not a sufficient condition, since other mechanisms may be devised which would also be consistent with these data. Much more convincing evidence is obtained from the fact that the mechanism predicts inversion of configuration when the substrate is optically active, and this has been observed many times. This inversion of configuration (see p. 85) is called the *Walden inversion* and was observed long before the S_N2 mechanism was formulated by Hughes and Ingold.[2]

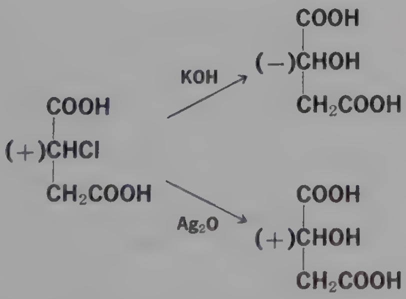
At this point it is desirable for us to see just how it was originally proved that a given substitution reaction proceeds with inversion of configuration, even before the mechanism was known. Walden presented a number of examples[3] in which inversion *must* have taken place. For example, (+)-malic acid could be converted to (+)-chlorosuccinic acid by thionyl chloride, and to (−)-chlorosuccinic acid by phosphorus pentachloride:

---

[2] Cowdrey, Hughes, Ingold, Masterman, and Scott, *J. Chem. Soc.* **1937**, 1252. The idea that the addition of one group and removal of the other are simultaneous was first suggested by Lewis in "Valence and the Structure of Atoms and Molecules," p. 113, Chemical Catalog Company, Inc., New York, 1923. The idea that a one-step substitution leads to inversion was proposed by Olsen, *J. Chem. Phys.* **1**, 418 (1933).



One of these must be an inversion and the other a retention of configuration, but the question is, which is which? The signs of rotation are of no help in answering this question since, as we have seen in Chapter 4 (p. 83), rotation need not be related to configuration. Another example discovered by Walden is



Once again, one reaction and only one must be an inversion, but which? It may also be noticed [illustrated by the use of thionyl chloride on (+)-malic acid and treatment of the product with KOH] that it is possible to convert an optically active compound into its enantiomer.[4]

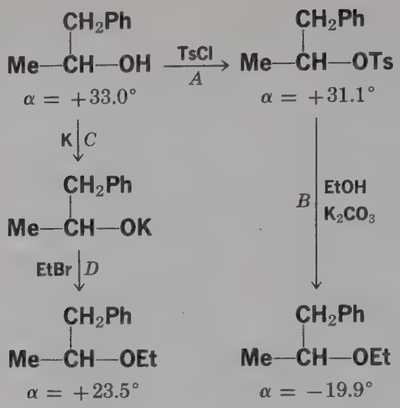
A series of experiments designed to settle the matter of exactly where inversion takes place was performed by Phillips, Kenyon, and coworkers. In 1923, Phillips carried out the following cycle:[5]

---

[3] Walden, *Ber.* **26**, 210 (1893), **29**, 133 (1896), **32**, 1855 (1899).

[4] The student may be wondering just what is the mechanism in those cases where retention of configuration is involved, since it is certainly not simple S_N2. As we shall see later, the reaction between malic acid and thionyl chloride is an S_Ni process (p. 268), while a neighboring-group mechanism (p. 263) is involved in the treatment of chlorosuccinic acid with silver oxide.

[5] Phillips, *J. Chem. Soc.* **123**, 44 (1923).



In this cycle, (+)-1-phenyl-2-propanol is converted to its ethyl ether by two routes: path *AB* giving the (−) ether, and path *CD* giving the (+) ether. Therefore, at least one of the four steps must be an inversion. It is extremely unlikely that there is inversion in steps *A*, *C*, or *D*, since in all of these steps the C—O bond is unbroken, and in none of them could the oxygen of the bond have come from the reagent. There is therefore a high probability that *A*, *C*, and *D* proceeded with retention of configuration, leaving *B* as the step involving inversion. A number of other such cycles were carried out, always with nonconflicting results.[6] These experiments not only definitely showed that certain specific reactions were proceeding with inversion, but also established the configurations of many compounds.

The Walden inversion has been found at a primary carbon atom (by the use of an optically active substrate containing a deuterium and a hydrogen atom at the carbon bearing the leaving group[7]) and at a sulfur (in sulfoxides),[8] a silicon,[9] and a phosphorus atom.[10]

Another kind of evidence for the S_N2 mechanism comes from compounds with potential leaving groups at bridgehead carbons. If the S_N2 mechanism is correct, these compounds should not be able to react by this mechanism, since the nucleophile cannot approach from the rear. Among the many known examples of unsuccessful reaction attempts at bridgeheads under S_N2 conditions[11] are the treatment of the [2.2.2] system **2** with ethoxide ion[12] and the treatment of the [3.3.1] system **3** with sodium iodide in acetone.[13] In these cases, open-chain analogs underwent the reactions readily. As a final example

---

[6] For example, see Kenyon, Phillips, and Turley, *J. Chem. Soc.* **127**, 399 (1925); Kenyon, Phillips, and Taylor, *J. Chem. Soc.* **1933**, 173; and Kenyon, Phillips, and Shutt, *J. Chem. Soc.* **1935**, 1663.

[7] Streitwieser, *J. Am. Chem. Soc.* **75**, 5014 (1953).

[8] Johnson and McCants, *J. Am. Chem. Soc.* **87**, 5404 (1965).

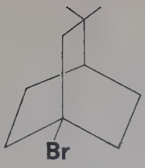
[9] Sommer, *Angew. Chem. Intern. Ed. Engl.* **1**, 143–148 (1962).

[10] Green and Hudson, *Proc. Chem. Soc.* **1962**, 307.

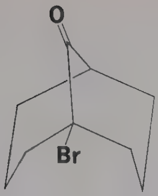
[11] For a review of reactions at bridgehead carbons, see Applequist and Roberts, *Chem. Rev.* **54**, 1065–1089 (1954).

[12] Doering, Levitz, Sayigh, Sprecher, and Whelan, *J. Am. Chem. Soc.* **75**, 1008 (1953). Actually, a slow substitution was observed in this case, but not by an S_N2 mechanism.

[13] Cope and Synerholm, *J. Am. Chem. Soc.* **72**, 5228 (1950).



2



3

of evidence for the S_N2 mechanism, the reaction between optically active 2-octyl iodide and radioactive iodide ion may be mentioned:

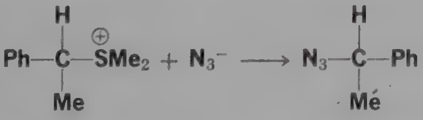
$$C_6H_{13}CHMeI + {}^{*}I^{-} \longrightarrow C_6H_{13}CHMe{}^{*}I + I^{-}$$

In this reaction, racemization is expected, since if we start with the pure D isomer, at first each exchange will produce an L isomer, but with increasing concentration of L isomer, *it* will begin to compete for I^- with the D isomer, until at the end a racemic mixture will be left, which will then remain at equilibrium. The point investigated was a comparison of the rate of inversion with the rate of uptake of radioactive $^{*}I^{-}$. It was found[14] that the rates were identical within experimental error:

Rate of inversion	$2.88 \pm 0.03 \times 10^{-5}$
Rate of exchange	$3.00 \pm 0.25 \times 10^{-5}$

What was actually measured was the rate of racemization, which is twice the rate of inversion, since each inversion creates, in effect, two racemic molecules. The significance of this result is that it shows that every act of exchange is an act of inversion.

It has now been shown that the S_N2 mechanism can operate in reactions of all four of the charge types shown on page 251, even in the case of Type III, where a negatively charged nucleophile must attack a positively charged substrate at a position in the molecule farthest away from the positive charge.[15] For example, the reaction between azide ion and dimethyl-1-phenylethylsulfonium chloride proceeds with complete inversion:



$$Ph\!-\!\underset{Me}{\overset{H}{C}}\!-\!\overset{\oplus}{S}Me_2 + N_3^- \longrightarrow N_3\!-\!\underset{Me}{\overset{H}{C}}\!-\!Ph$$

In reactions of Type III it might have been expected that the negative nucleophile would directly attack the side occupied by the positively charged group.

---

[14] Hughes, Juliusburger, Masterman, Topley, and Weiss, *J. Chem. Soc.* **1935**, 1525.

[15] Harvey, Hoye, Hughes, and Ingold, *J. Chem. Soc.* **1960**, 800; Hughes and Whittingham, *J. Chem. Soc.* **1960**, 806; Hoffmann and Hughes, *J. Chem. Soc.* **1964**, 1252, 1259.

The S_N1 Mechanism. The most ideal version of the S_N1 mechanism (substitution nucleophilic unimolecular) consists of two steps (once again, possible charges on the substrate and nucleophile are not shown):

$$1.\quad R{-}X \xrightleftharpoons{\text{slow}} R^+ + X$$

$$2.\quad R^+ + Y \xrightarrow{\text{fast}} R{-}Y$$

The first step is a slow ionization of the substrate and is the rate-determining step. The second step is a rapid reaction between the intermediate carbonium ion and the nucleophile. Actually the ionization is always assisted by the solvent.

In looking for evidence for the S_N1 reaction, the first thought is that it should be a first-order reaction following the rate law

$$\text{Rate} = k[\text{RX}] \tag{3}$$

Since the slow step involves only the substrate, the rate should be dependent only on that. Although the solvent is necessary to assist in the process of ionization, it does not enter the rate expression, since it is present in large excess. However, the simple rate law given [Eq. (3)] is not sufficient to account for all the data. Many cases are known where pure first-order kinetics are followed, but in many other cases this is not so. We may explain this by taking into account the reversibility of the first step of the reaction. The X formed in this step competes with Y for the substrate, and the rate law must be modified as follows (see Chapter 7):

$$\text{RX} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{R}^+ + \text{X}$$

$$\text{R}^+ + \text{Y} \xrightarrow{k_2} \text{RY}$$

$$\text{Rate} = \frac{k_1k_2[\text{RX}][\text{Y}]}{k_{-1}[\text{X}] + k_2[\text{Y}]} \tag{4}$$

At the beginning of the reaction, when the concentration of X is very small, $k_{-1}[\text{X}]$ is negligible compared to $k_2[\text{Y}]$, and the rate law is reduced to Eq. (3). Indeed, S_N1 reactions generally do display simple first-order kinetics in their initial stages. Most kinetic studies of S_N1 reactions have been carried out on solvolytic reactions, since most S_N1 reactions fall into this category. In the later stages of S_N1 solvolyses, [X] becomes large, and Eq. (4) predicts that the rate should decrease. This is found to be the case for diarylmethyl halides,[16] though not for *tert*-butyl halides, which follow Eq. (3) for the entire reaction.[17] An explanation for this difference is that *tert*-butyl cations are more reactive than the relatively stable diarylmethyl type (p. 128) and hence less selective. Although halide ion is a much more powerful nucleophile than water, there is much more water available, since it is the solvent.[18]

---

[16] Benfy, Hughes, and Ingold, *J. Chem. Soc.* **1952,** 2488.

[17] Bateman, Hughes, and Ingold, *J. Chem. Soc.* **1940,** 960.

[18] Actually, in the experiments mentioned the solvent was "70%" or "80%" aqueous acetone. "80%" aqueous acetone consists of four volumes of dry acetone and one volume of water.

The selective benzhydryl cation survives many collisions with solvent molecules before combining with a reactive halide, but the less selective *tert*-butyl ion cannot wait for a reactive but relatively rare halide ion and combines with the solvent.

If the X formed during the reaction can decrease the rate, at least in some cases, it should be possible to *add* X from the outside and further decrease the rate in that way. This retardation of rate by addition of X is called the *common-ion effect,* or the *mass-law effect.* Once again, addition of halide ions does decrease the rate for benzhydryl but not for *tert*-butyl halides. Evidence that the common-ion effect operates even with *tert*-butyl halides is that, when *tert*-butyl chloride was hydrolyzed in the presence of $^{36}Cl^-$ (which is radioactive), radioactive *tert*-butyl chloride was detected.[19]

One factor which complicates the kinetic picture is the *salt effect.* An increase of ionic strength of the solution usually increases the rate of an S_N1 reaction (p. 295). But when the reaction is of charge type II, where both Y and RX are neutral, so that X is negatively charged (and most solvolyses are of this charge type), then the ionic strength increases as the reaction proceeds, and this increases the rate. This effect must be taken into account in studying the kinetics.

It may be noted that the pseudo-first-order rate law for an S_N2 reaction in the presence of a large excess of Y [Eq. (2)] is the same as that for an ordinary S_N1 reaction [Eq. (3)]. It is thus not possible to tell these cases apart by simple kinetic measurements. However, we can often distinguish between them by the common-ion effect, mentioned above. Addition of a common ion will not markedly affect the rate of an S_N2 reaction beyond the effect caused by other ions. Unfortunately, as we have seen above, not all S_N1 reactions show the common-ion effect, and this test fails for *tert*-butyl and similar cases.

Kinetic studies also provide other evidence for the S_N1 mechanism. If this mechanism is operating essentially as shown on page 256, then the rate should be the same for a given substrate under a given set of conditions, *regardless of the identity of the nucleophile or of its concentration.* One experiment which demonstrated this was carried out by Bateman, Hughes, and Ingold.[20] In this experiment benzhydryl chloride was treated in SO_2 with the nucleophiles fluoride ion, pyridine, and triethylamine, at several concentrations of each nucleophile. In each case the initial rate of the reaction was approximately the same, when corrections were made for the salt effect. The same type of behavior has been shown in a number of other cases, even when the reagents are as different in their nucleophilicities (see p. 287) as H_2O and OH^-.

The stereochemical evidence is also more equivocal than it is for the S_N2 reaction. If there is a free carbonium ion, it is planar (see p. 129), and the nucleophile should attack with equal facility from either side of the plane. This should result in complete racemization. Although many first-order substitutions do give complete racemization, many others do not. Typically there is 5 to 20% inversion. There are several possible explanations for this:

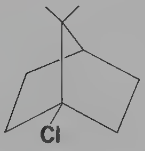
---

[19] Bunton and Nayak, *J. Chem. Soc.* **1959,** 3854.

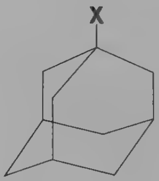
[20] Bateman, Hughes, and Ingold, *J. Chem. Soc.* **1940,** 1011.

the carbonium ion may not be completely free, or it may have a lifetime so short that it does not have time to attain planarity before the nucleophile attacks. Both of these effects may be present at once: if the carbonium ion has a very short lifetime, then the arrival of the nucleophile will find the leaving group still in the vicinity and able to block attack from that direction. These explanations have led to the idea of reactions intermediate between S_N1 and S_N2, which will be considered in the next section. For a long time, belief in the S_N1 mechanism was held up because many workers did not accept the idea of carbonium ions (even solvated). However, there is no longer any doubt about their existence (see Chapter 5).

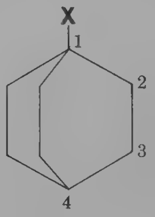
Further evidence for the S_N1 mechanism is that reactions run under S_N1 conditions fail, or proceed very slowly, at bridgehead positions.[11] S_N2 reactions also fail with these substrates (p. 254), though for a different reason. If S_N1 reactions require carbonium ions and if carbonium ions must be planar or nearly planar, then it is no surprise that bridgehead carbon atoms, which cannot assume planarity, do not become the seat of carbonium ions. As an example, 1-chloroapocamphane (**4**), boiled 21 hr with 30% KOH in 80% ethanol, or 48 hr with aqueous ethanolic silver nitrate, gave no reaction in either case,[21] although analogous open-chain systems reacted readily. According to this theory, if the rings are large enough, S_N1 reactions should be possible, since near-planar carbonium ions might be expected there. This does turn out to be the case. For example, [2.2.2] bicyclic systems undergo S_N1 reactions much faster than smaller bicyclic systems, though the reaction is still slower than with open-chain systems. 1-Substituted adamantane compounds (**5**) present an anomaly, since they have been found to undergo S_N1 reactions about 5×10^3 times faster than [2.2.2] systems (**6**) (though the reaction is again still slower than in open-chain systems),[22] though the geometry near the leaving group is the same. It may be that **5** can form a carbonium ion more easily than **6** because repulsion between C-1 and C-4 of **6** is not present in **5**, so that it is easier for **5** to flatten out.[22] Positive evidence that the 1-adamantyl cation can exist, despite the fact that the positive charge is at a bridgehead, was obtained by its isolation as the SbF_6^- salt:[23]



4



5



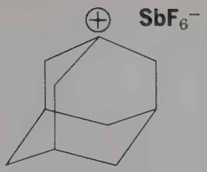
6

---

[21] Bartlett and Knox, *J. Am. Chem. Soc.* **61**, 3184 (1939).

[22] Schleyer and Nicholas, *J. Am. Chem. Soc.* **83**, 2700 (1961); Fort and Schleyer, *J. Am. Chem. Soc.* **86**, 4194 (1964).

[23] Schleyer, Fort, Watts, Comisarow, and Olah, *J. Am. Chem. Soc.* **86**, 4194 (1964).



It has been proposed[24] that S_N1 reactions proceed in this manner:

$$\mathrm{R{-}X} \rightleftharpoons \underset{\mathbf{7}}{\mathrm{R^+\quad X^-}} \rightleftharpoons \underset{\mathbf{8}}{\mathrm{R^+\|X^-}} \rightleftharpoons \underset{\mathbf{9}}{\mathrm{R^+ + X^-}}$$

where **7** is an "intimate" ion pair, **8** a solvent-separated ion pair, and **9** the dissociated ions (each presumably surrounded by molecules of solvent), and that reaction products may result from attack by the nucleophile at any stage. This could provide an explanation of partial inversion, since in the intimate-ion-pair stage the carbonium ion might still retain its original configuration. The reaction in which the intimate ion pair recombines to give the original substrate is referred to as "*internal return*." Internal return may involve racemization, although it has been shown that at least in some cases there is partial or even complete retention of configuration.[25] Evidence for the intermediacy of ion pairs in S_N1 reactions comes from the *special salt effect*. The addition of $LiClO_4$ or LiBr in the acetolysis of certain tosylates produced an initial steep rate acceleration which then decreased to the normal linear acceleration (caused by the ordinary salt effect).[26] This is interpreted as follows: the ClO_4^- (or Br^-) is trapping the solvent-separated ion pair to give $R^+ \| ClO_4^-$, which, being unstable under these conditions, goes to product. Hence, the amount of solvent-separated ion pair which would have returned to the starting material is reduced, and the rate of the overall reaction is increased. This amounts to shifting the position of the equilibrium by removing a product. There is much other evidence for the ion-pair concept. For example, optically active *p*-chlorobenzhydryl chloride racemizes about thirty times faster than it solvolyzes in acetic acid.[27] In this case internal return racemizes the substrate. However, when the leaving group is the same as the solvent (for example, ROAc in HOAc), racemization is only slightly faster than solvolysis.[28]

It has been suggested that ion pairs are intermediates in the few known cases in which S_N1 mechanisms proceed with retention of configuration (in the absence of a neighboring group; see p. 263).[29] For example, it is proposed that the phenolysis of optically active α-phenylethyl chloride, in which the ether of retained configuration is obtained, involves a four-center mechanism:

---

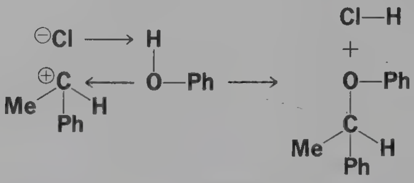
[24] Winstein, Clippinger, Fainberg, Heck, and Robinson, *J. Am. Chem. Soc.* **78,** 328 (1956).

[25] Goering and Levy, *J. Am. Chem. Soc.* **86,** 120 (1964); Goering and Chang, *Tetrahedron Letters* **1965,** 3607. Also see below (Ref. 28).

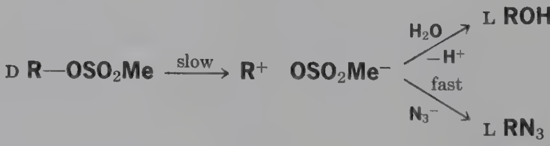
[26] Ref. 24; Winstein, Klinedinst, and Clippinger, *J. Am. Chem. Soc.* **83,** 4986 (1961).

[27] Winstein, Hojo, and Smith, *Tetrahedron Letters* **1960,** No. 22, 12; Winstein, Gall, Hojo, and Smith, *J. Am. Chem. Soc.* **82,** 1010 (1960); Winstein and Gall, *Tetrahedron Letters* **1960,** No. 2, 31. Also see Kohnstam and Shillaker, *J. Chem. Soc.* **1959,** 1915; Winstein, Baker, and Smith, *J. Am. Chem. Soc.* **86,** 2073 (1964); and Streitwieser and Walsh, *J. Am. Chem. Soc.* **87,** 3686 (1965).

[28] Diaz and Winstein, *J. Am. Chem. Soc.* **86,** 4484 (1964).



Ion pairs have also been implicated in at least some reactions which would generally be called S_N2 reactions. Evidence is as follows: solvolysis of optically active 2-octyl methanesulfonate in 25% aqueous dioxane gave 2-octanol with about 95% inversion of configuration. From this fact the mechanism is regarded as S_N2, although it cannot be shown to be second order, because the nucleophile is present in large excess. Addition of 0.0462 *M* azide ions had no effect on the rate of the solvolysis (the rate of disappearance of the starting sulfonate), even though 31% of the product was now 2-octyl azide (the other 69% was inverted alcohol).[30] This means that azide ion is not involved in the rate-determining step, so it would seem that the mechanism of azide formation could not be S_N2. *Yet the configuration of the 2-octyl azide was about* 81% *inverted.* It may be concluded that the rate-determining step is formation of the ion pair, which in this case maintains its configuration, and that this is what is attacked either by azide or by the solvent water. Consequently, not only is azide absent from the transition state, but so is water:



This result, along with others, has led to the conclusion that an ion pair is a common intermediate for S_N1 and S_N2 reactions, "its formation being rate-determining in the former case and its destruction being rate-determining in the latter."[30]

The difference between the S_N1 and S_N2 mechanisms is in the timing of the steps. In the S_N1 mechanism, first X leaves, then Y attacks. In the S_N2 case, the two things happen simultaneously. One could imagine the third possibility: first the attack of Y, and then the removal of X. This is not possible at a saturated carbon, since it would mean more than eight electrons in the outer shell of carbon. However, this type of mechanism is possible and indeed occurs at other types of substrate (pp. 274–278; Chapter 13).

---

[29] Okamoto, Yamada, Nitta, and Shingu, *Bull. Chem. Soc. Japan* **39**, 299 (1966); Okamoto, Hayashi, and Shingu, *Bull. Chem. Soc. Japan* **39**, 408 (1966).

[30] Weiner and Sneen, *J. Am. Chem. Soc.* **87**, 292 (1965). See also Sneen and Larsen, *J. Am. Chem. Soc.* **88**, 2593 (1966).

Mixed S_N1 and S_N2 Mechanisms. Some reactions of a given substrate under a given set of conditions display all the characteristics of S_N2 mechanisms; other reactions seem to proceed by S_N1 mechanisms, but often there are found cases which cannot be characterized so easily. There seems to be something in between, a mechanistic "borderline" region. At least two theories have been devised to explain these phenomena. Swain postulated[31] that there is only one type of mechanism, of which the S_N1 and S_N2 represent extremes. In all cases there is a pushing of the leaving group by the nucleophile and a pulling of it by the solvent. In a "pure" S_N1 case there is little or no push, in a "pure" S_N2 case little or no pull, but many reactions may be affected both by the nucleophile and the solvent. However, there is no suggestion that the pushing and pulling must in all cases be simultaneous.[32] Evidence for this argument is that, in a benzene solvent, when triphenylmethyl chloride is treated with both methanol and phenol, the reaction is first order *in each component* (overall third order), although the only product is methoxytriphenylmethane. This indicates that both the nucleophile (methanol) and the added phenol are playing roles, and the most likely role of the phenol is to assist in removal of the leaving group. Also, phenols containing ortho substituents which could form hydrogen bonds with the phenolic OH group and thus decrease its solvolyzing power, catalyzed the reaction much less than similar phenols with para substituents.[33]

However, others hold that there are two types of mechanism, S_N1 and S_N2, and that "borderline" behavior is caused simply by both mechanisms operating simultaneously on the same substrate; that is, some molecules are reacting by the S_N1 mechanism, while others in the same reaction vessel are giving the same products by the S_N2 mechanism. There is some strong evidence for this view. One example was found by a study of the behavior of 4-methoxybenzyl chloride in 70% aqueous acetone.[34] In this solvent, hydrolysis (that is, conversion to 4-methoxybenzyl alcohol) occurs by an S_N1 mechanism. When azide ions are added, the alcohol is still a product, but now 4-methoxybenzyl azide is another product. Addition of azide ions increases the rate of ionization (by the salt effect) but *decreases* the rate of hydrolysis. If more carbonium ions are being produced but fewer go to the alcohol, then some azide must be formed by reaction with carbonium ions—an S_N1 process. However, the rate of ionization is always *less* than the total rate of reaction, so that some azide must also be forming by an S_N2 mechanism. Thus, S_N1 and S_N2 mechanisms are operating simultaneously.

Some nucleophilic substitution reactions which seem to involve a "borderline" mechanism actually do not. Thus, one of the principal indications that a "borderline" mechanism is taking place has been the finding of partial racemization and partial inversion. However, Weiner and Sneen have demonstrated that this type of stereochemical behavior is quite consistent with a strictly S_N2 process. These workers studied the reaction of optically active 2-octyl brosylate in 75% aqueous dioxane, under which conditions inverted 2-octanol was obtained in 77% optical purity.[35] When sodium azide was added, 2-octyl azide was obtained along with the 2-octanol, *but the latter was now 100% inverted.* It is apparent that, in the original case, 2-octanol was being produced by two different processes, an S_N2 reaction leading to inverted product, and another process in which some intermediate leads to racemization or retention. When azide ions were added, they scavenged this intermediate, so that the entire second process now went to produce azide, while the S_N2 reaction, unaffected by the addition of azide, still went on to give inverted 2-octanol. What is the nature of the intermediate in the second process? At first thought we might suppose that it is a carbonium ion, so that this would be another example of simultaneous S_N1 and S_N2 reactions. However, solvolysis of 2-octyl brosylate in pure methanol, or of 2-octyl methanesulfonate in pure water, in the absence of azide ions, gave methyl 2-octyl ether, or 2-octanol, respectively, *with* 100% *inversion of configuration,* indicating that the mechanism in these solvents was pure S_N2. Since methanol and water are more polar than 75% aqueous dioxane and since an increase in polarity of solvent increases the rate of S_N1 reactions at the expense of S_N2 (p. 293), it is extremely unlikely that any S_N1 process could be occurring in 75% aqueous dioxane. The intermediate in the second process is thus not a carbonium ion. What it is, is suggested by the fact that, in the absence of azide ions, the amount of inverted 2-octanol decreased with an increasing percentage of dioxane in the solvent. Thus the intermediate is an oxonium ion, formed by an S_N2 attack *by dioxane.* This ion is not a stable product but reacts with water in another S_N2 process to produce 2-octanol with retained configuration. The entire process may be shown as follows:

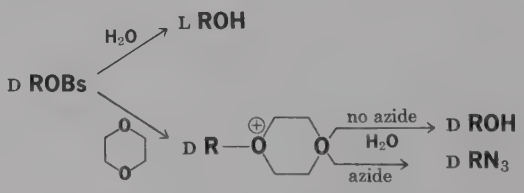
---

[31] Swain, *J. Am. Chem. Soc.* **70,** 1119 (1948); Swain and Eddy, *J. Am. Chem. Soc.* **70,** 2989 (1948).

[32] Swain and Pegues, *J. Am. Chem. Soc.* **80,** 812 (1958); Andrews and Keefer, *J. Am. Chem. Soc.* **83,** 3708 (1961).

[33] Okamoto and Shingu, *Bull. Chem. Soc. Japan* **34,** 1131 (1961); Okamoto, Takeuchi, and Shingu, *Bull. Chem. Soc. Japan* **34,** 1137 (1961).

[34] Kohnstam, Queen, and Shillaker, *Proc. Chem. Soc.* **1959,** 157. Other evidence may be found in Pocker, *J. Chem. Soc.* **1959,** 3939, 3944; Casapieri and Swart, *J. Chem. Soc.* **1961,** 4342, **1963,** 1254; Fava, Iliceto, and Ceccon, *Tetrahedron Letters* **1963,** 685; and Okamoto, Uchida, Saitô, and Shingu, *Bull. Chem. Soc. Japan* **39,** 307 (1966).



That part of the original reaction which resulted in retention of configuration is thus seen to stem from two successive S_N2 reactions, and not from any "borderline" behavior.[36] In another investigation, Streitwieser, Walsh, and Wolfe showed that the racemization accompanying inversion in the acetolysis of optically active 2-octyl tosylate stems from processes other than the actual solvolytic displacement: from reaction of the product 2-octyl tosylate with the *p*-toluenesulfonic acid also formed; from addition of acetic acid to 2-octene (formed from the substrate by a competing elimination reaction); and from racemization of the starting tosylate.[37] The actual nucleophilic substitution

---

[35] Weiner and Sneen, *J. Am. Chem. Soc.* **87**, 287 (1965).

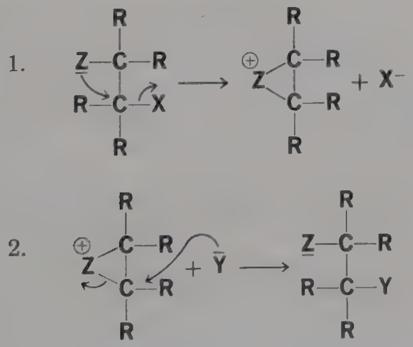
[36] According to this scheme, the configuration of the isolated RN_3 should be retained. It was, however, largely inverted, owing to a competing S_N2 reaction where N_3^- directly attacks ROBs.

$$\mathrm{ROTs + HOAc \longrightarrow ROAc}$$

proceeds with essentially complete inversion of configuration.

The mechanisms so far considered can, in theory at least, operate on any type of saturated (or for that matter unsaturated) substrate. There are other mechanisms which are more limited in scope.

The Neighboring-group Mechanism.[38] It is occasionally found with certain substrates that (1) the rate of reaction is greater than expected, and (2) the configuration at an asymmetric center is *retained* and not inverted or racemized. In these cases there is usually a group with an unshared pair of electrons β to the leaving group (or sometimes farther away). The mechanism operating in such cases is called the *neighboring-group mechanism* and consists essentially of two S_N2 substitutions, each causing an inversion, so that the net result is retention of configuration. In the first step of this reaction the neighboring group acts as a nucleophile, pushing out the leaving group, but still retaining attachment to the molecule. In the second step the external nucleophile pushes out the neighboring group:



The reaction obviously must go faster than if Y were attacking directly, since if the latter process were faster, *it* would be happening. The neighboring group Z is said to be lending *anchimeric assistance*. The rate law followed in the neighboring-group mechanism is the first-order law shown in Eq. (2) or (3); that is, Y does not take part in the rate-determining step.

The question may be asked as to why attack by Z is faster than that by Y. The answer is that the group Z is more available. In order for Y to react, it must collide with the substrate, but Z is immediately available, by virtue of its position. A reaction between the substrate and Y involves a decrease in entropy, since the reactants are far less free in the transition state than before. Reaction of Z involves a much smaller loss of entropy.

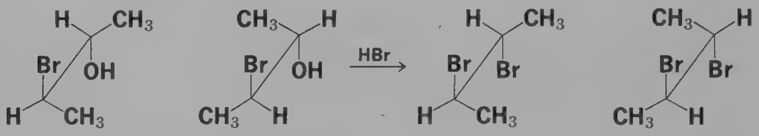
---

[37] Streitwieser, Walsh, and Wolfe, *J. Am. Chem. Soc.* **87**, 3682 (1965); Streitwieser and Walsh, *J. Am. Chem. Soc.* **87**, 3686 (1965).

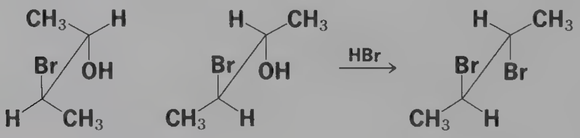
[38] For a review, see Capon, *Quart. Rev.* (*London*) **18**, 45–111 (1964).

It is not always easy to determine when a reaction rate has been increased by anchimeric assistance. In order to be certain, it is necessary to know what the rate would be without participation by the neighboring group. The obvious way to examine this question is to compare the rates of the reaction with and without the neighboring group, for example, $HOCH_2CH_2Br$ versus CH_3CH_2Br. However, this will certainly not give an accurate determination of the extent of participation, since the inductive and steric effects of H and OH are not the same. Because of this, it is desirable to have a large increase in the rate, preferably more than fiftyfold, before a rate increase is attributed to neighboring-group participation.

The first important evidence for the existence of this mechanism was the demonstration that retention of configuration can occur if the substrate is suitable. It was shown that the threo DL pair of 3-bromo-2-butanol when treated with HBr gave DL-2,3-dibromobutane, while the erythro pair gave the meso isomer.[39]

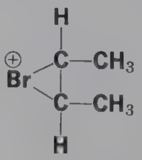


Threo DL pair DL pair



Erythro DL pair Meso

This indicated that retention had taken place. Note that both products are optically inactive and so cannot be told apart by differences in rotation. The meso and DL dibromides have different boiling points and indexes of refraction and were identified by these properties. Even more convincing evidence was that either of the two threo isomers alone gave not just one of the enantiomeric dibromides, but the DL pair. The reason for this is that the intermediate present after the attack by the neighboring group (**10**) is



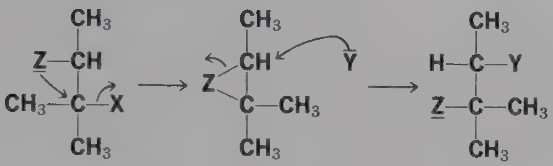
10

---

[39] Winstein and Lucas, *J. Am. Chem. Soc.* **61**, 1576, 2845 (1939).

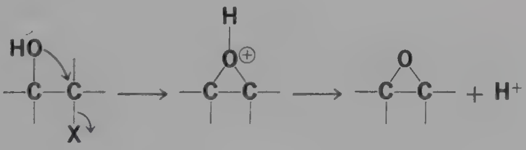
symmetrical, so that the external nucleophile, Br^-, could equally well attack both carbon atoms. **10** is a bromonium ion, the existence of which has been demonstrated in several types of reaction[40] and which we shall meet again.

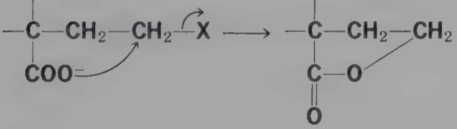
Although **10** is symmetrical, intermediates in most neighboring-group mechanisms are not, and it is therefore possible to get, not a simple substitution product, but a rearrangement. This will happen if Y attacks not the carbon atom from which X left, but the one to which Z was originally attached:



In such cases substitution and rearrangement products are often produced together. For a discussion of rearrangements, see Chapter 18.

Another possibility is that the intermediate may be stable or may find some other way to stabilize itself. In such cases, Y never attacks at all, and the product is cyclic. These reactions amount to internal S_N2 reactions and will only occur if the ring size is right. Two examples are epoxide formation and lactone formation:



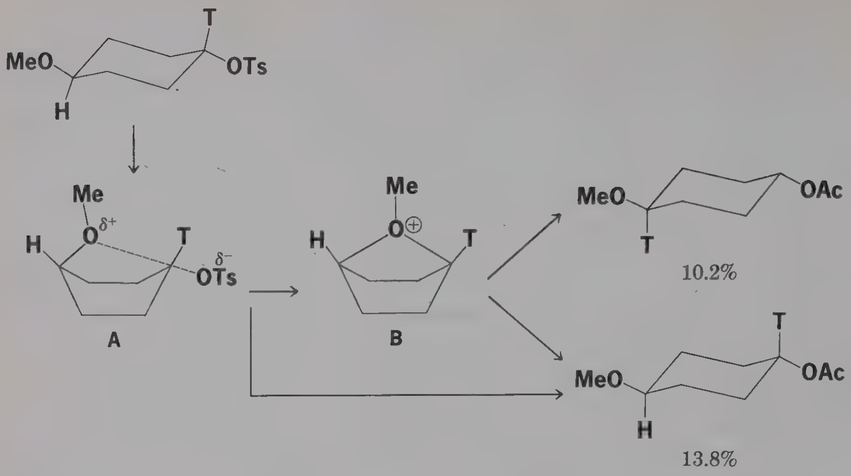


There is evidence that a neighboring group need not form a completely covalent bond with the substrate carbon in order to lend anchimeric assistance. Thus Noyce and coworkers showed that *trans*-4-methoxy[1-^{3}H]-cyclohexyl tosylate when subjected to acetolysis gave 24% *trans*-4-methoxycyclohexyl acetate with 35% more tritium in the 1-position than in the 4-position.[41] If all of the trans product came from the intermediate **B**, which is fully covalently bonded, then the tritium would have been equally distributed between the 1- and the 4-positions, except for the small isotope effect, by which, if anything, more tritium would be expected in the 4-position. The excess 1-tritiated acetate could not have come from an ordinary S_N2 reaction,

---

[40] See Traynham, *J. Chem. Educ.* **40,** 392 (1963).

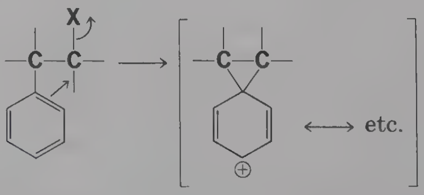
[41] Noyce, Thomas, and Bastian, *J. Am. Chem. Soc.* **82,** 885 (1960); Noyce and Bastian, *J. Am. Chem. Soc.* **82,** 1246 (1960).



since in that case the configuration would have been inverted. Indeed, 9.6% of *cis*-4-methoxycyclohexyl acetate (all labeled in the 1-position) was isolated in this reaction, formed by a concurrent S_N2 reaction. Noyce and coworkers were thus led to postulate the intermediacy of an ion pair (**A**) which could go to **B** or directly to the substitution product.

The neighboring-group mechanism operates only when the ring size is right for a particular type of Z. For example, for $MeO(CH_2)_nOBs$, neighboring-group participation was important for $n = 4$ or 5 (corresponding to a five- or six-membered intermediate) but not for $n = 2$, 3, or 6.[42] However, optimum ring size is not the same for all reactions, even with a particular Z. In general, the most rapid reactions occur when the ring size is three, five, or six, depending on the reaction type.

The following are some of the more important neighboring groups with unshared pairs: COO^- (but not COOH), OCOR, COOR, OR, OH, O^-, NH_2, NHR, NR_2, NHCOR, SH, SR, S^-,[43] Br, and I (but not Cl). However, an unshared pair is not required for neighboring-group participation. When the phenyl group participates, a nonclassical-carbonium-ion intermediate (see p. 134) may be formed:

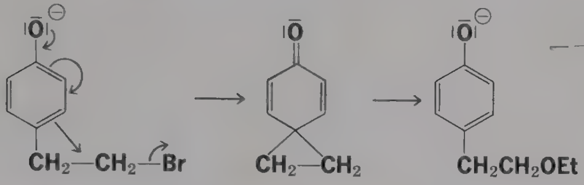


Participation by an aryl group is particularly important when it contains O^- in the para position. Thus, ethanolysis of the conjugate base of 2-(*p*-hydroxyphenyl)ethyl bromide is about 10^6 times faster than that of 2-(*p*-methoxyphenyl)ethyl bromide, where the intermediate is not so stable.[44]

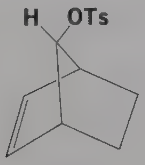
---

[42] Winstein, Allred, Heck, and Glick, *Tetrahedron* **3**, 1 (1958).

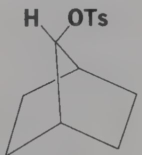
[43] For a review of sulfur-containing neighboring groups, see Gundermann, *Angew. Chem. Intern. Ed. Engl.* **2**, 674–683 (1963).



There has been controversy as to whether a C=C double bond can act as a neighboring group, but the evidence is that it can. For example, the acetolysis of **11** is 10^{11} times faster than that of **12,** and *proceeds with retention of configuration.*[45] Nonclassical carbonium ions (of the types **8** and **10** in Chapter 5, p. 130) are involved in this case too. In the cases just mentioned the aryl group and the double bond are located one carbon away from the leaving group (in the homoallylic position), but there is much evidence that these groups can also lend anchimeric assistance from positions farther away.[46]

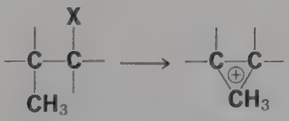


11



12

The phenyl and C=C groups do not have an unshared pair, but do have electrons in π orbitals, which may behave as Lewis bases (this is essentially their role as neighboring groups). But arguments have been advanced that alkyl groups, cycloalkyl groups,[47] and even hydrogen can behave as neighboring groups. For alkyl groups the process would be



13

---

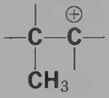
[44] Baird and Winstein, *J. Am. Chem. Soc.* **84,** 788 (1962), **85,** 567 (1963).

[45] Winstein and Shatavsky, *J. Am. Chem. Soc.* **78,** 592 (1956). For other evidence, see Shoppee, *J. Chem. Soc.* **1946,** 1138; LeBel and Huber, *J. Am. Chem. Soc.* **85,** 3193 (1963); and Closson and Kwiatkowski, *Tetrahedron* **21,** 2779 (1965).

[46] See Heck and Winstein, *J. Am. Chem. Soc.* **79,** 3105 (1957); LeNy, *Compt. rend.* **251,** 1526 (1960); Goering and Closson, *J. Am. Chem. Soc.* **83,** 3511 (1961); Lawton, *J. Am. Chem. Soc.* **83,** 2399 (1961); Winstein and Carter, *J. Am. Chem. Soc.* **83,** 4485 (1961); Bartlett, Bank, Crawford, and Schmid, *J. Am. Chem. Soc.* **87,** 1288 (1965); Bartlett and Sargent, *J. Am. Chem. Soc.* **87,** 1279 (1965); Bartlett, Trahanovsky, Bolon, and Schmid, *J. Am. Chem. Soc.* **87,** 1314 (1965); Bly and Swindell, *J. Org. Chem.* **30,** 10 (1965).

[47] Sneen, Lewandowski, Taha, and Smith, *J. Am. Chem. Soc.* **83,** 4843 (1961); Borčić, Nikoletić, and Sunko, *J. Am. Chem. Soc.* **84,** 1615 (1962).

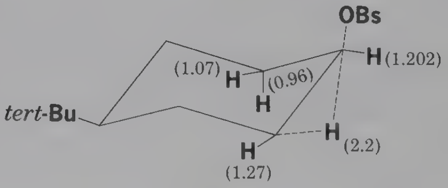
The arguments for the participation of alkyl groups are related to those for the existence of electron-deficient nonclassical carbonium ions (p. 136), so that they will not be further considered in this chapter, except to say that, if **13** is a possibility, then by loss of a proton, a cyclopropyl ring should be obtained. About 10% cyclopropane was recovered in a reaction where the propyl cation was an expected intermediate.[48] Since alkyl groups are common migrating groups in rearrangement reactions, **13** must lie on the reaction path, but this does not necessarily mean that the alkyl group acts as a neighboring group, that is, lends anchimeric assistance. It is entirely possible that the leaving group might cleave first to give



$$-\overset{|}{\underset{CH_3}{C}}-\overset{\oplus}{\underset{|}{C}}-$$

and that *then* **13** might form, either as an intermediate or a transition state. Indeed, many such rearrangements do not show the enhanced rates expected from anchimeric assistance.

There is strong evidence that hydrogen can lend anchimeric assistance to the departure of the leaving group, that is, act as a neighboring group. Solvolysis was carried out on *cis*-4-*tert*-butylcyclohexyl brosylate substituted with deuterium in the α position or in one or more of the β positions.[49] In this compound, the large *tert*-butyl group forces the brosylate group to be in the axial position. The isotope effect of one of the β hydrogens, an axial one, was much greater than that of a hydrogen at any other position, even the other axial β hydrogen. This indicates that this hydrogen participates in the transition state:



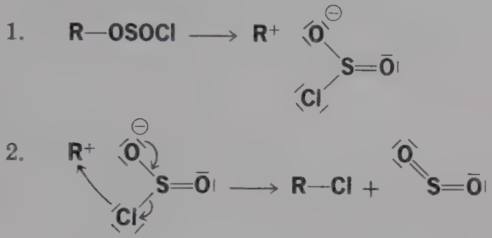
The two axial β hydrogens are equivalent, but only one gives rise to a large isotope effect when substituted by deuterium. This was determined by calculations using isotope-effect data from mono- and polydeuterated substrates. The isotope effect at each position is indicated on the diagram.

The S_Ni Mechanism. In a few reactions, nucleophilic substitutions proceed with retention of configuration even where there is no possibility of a neighboring-group effect. In the S_Ni mechanism (*substitution nucleophilic internal*) there must be a part of the leaving group which can attack the substrate, detaching itself from the rest of the leaving group in the process. The first step is the same as the very first step of the S_N1 mechanism: dissociation into an intimate ion pair. But in the second step a part of the leaving group attacks, necessarily from the front, since it is unable to get to the rear. This results in retention of configuration:

---

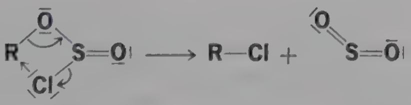
[48] Skell and Starer, *J. Am. Chem. Soc.* **82**, 2971 (1960); Silver, *J. Am. Chem. Soc.* **82**, 2971 (1960). See also Lee and Kruger, *Tetrahedron* **23**, 2539 (1967).

[49] Shiner and Jewett, *J. Am. Chem. Soc.* **87**, 1382 (1965). For other evidence from isotope effects, see Winstein and Takahashi, *Tetrahedron* **2**, 316 (1958).

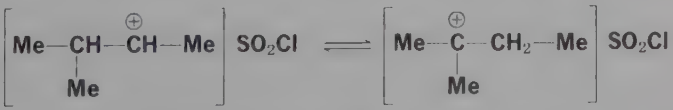


The example shown is the most important case of this mechanism yet discovered, since the reaction of alcohols with thionyl chloride to give alkyl halides proceeds in this way, with the first step in this case being $\mathrm{ROH + SOCl_2 \longrightarrow ROSOCl}$ (these alkyl chlorosulfites can be isolated).

Evidence for this mechanism is as follows: the addition of pyridine to the mixture of alcohol and thionyl chloride results in the formation of alkyl halide with *inverted* configuration. Inversion results because the pyridine reacts with ROSOCl to give $\mathrm{ROSO\overset{\oplus}{N}C_5H_5}$ before anything further can take place. The $\mathrm{Cl^-}$ freed in this process now attacks from the rear. The reaction between alcohols and thionyl chloride is second order, which is predicted by this mechanism, but the decomposition by simple heating of ROSOCl is first order.[50] It was previously believed that the reaction was a one-step process:



However, the fact that $\mathrm{Me_2CHCHMeOSOCl}$ gave, upon heating, $\mathrm{Me_2CClCH_2Me}$[51] indicated that an ion pair must have been present, since there is no other way to account for the rearrangement:



$$\left[\mathrm{Me{-}\underset{\displaystyle Me}{\underset{|}{CH}}{-}\overset{\oplus}{C}H{-}Me}\right]\mathrm{SO_2Cl} \rightleftharpoons \left[\mathrm{Me{-}\underset{\displaystyle Me}{\underset{|}{\overset{\oplus}{C}}}{-}CH_2{-}Me}\right]\mathrm{SO_2Cl}$$

The S_Ni mechanism is relatively rare, another example of it being the decomposition of ROCOCl (alkyl chloroformates) into RCl and $\mathrm{CO_2}$.[52]

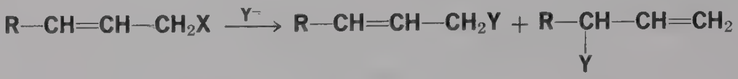
---

[50] Lewis and Boozer, *J. Am. Chem. Soc.* **74**, 308 (1952).

[51] Lee and Finlayson, *Can. J. Chem.* **39**, 260 (1961); Lee, Clayton, Lee, and Finlayson, *Tetrahedron* **18**, 1395 (1962).

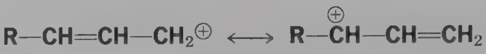
[52] Lewis and Herndon, *J. Am. Chem. Soc.* **83**, 1955 (1961); Lewis, Herndon, and Duffey, *J. Am. Chem. Soc.* **83**, 1959 (1961). For other examples, see Hart and Elia, *J. Am. Chem. Soc.* **83**, 985 (1961); Stevens, Munk, Ash, and Elliot, *J. Am. Chem. Soc.* **85**, 3390 (1963); and Stevens, Dittmer, and Kovacs, *J. Am. Chem. Soc.* **85**, 3394 (1963).

Nucleophilic Substitution at an Allylic Carbon. Allylic Rearrangements.[53] Allylic substrates undergo nucleophilic substitution reactions especially rapidly (see p. 283), but we discuss them in a separate section because they are usually accompanied by a certain kind of rearrangement, known as an *allylic rearrangement,* or an *allylic shift.* When allylic substrates are treated with nucleophiles under S_N1 conditions, two products are usually obtained: the normal one and a rearranged one.



$$R{-}CH{=}CH{-}CH_2X \xrightarrow{Y^-} R{-}CH{=}CH{-}CH_2Y + R{-}\underset{\displaystyle Y}{\underset{|}{C}H}{-}CH{=}CH_2$$

Two products are formed because an allylic type of carbonium ion is a resonance hybrid



$$R{-}CH{=}CH{-}CH_2^{\oplus} \longleftrightarrow R{-}\overset{\oplus}{C}H{-}CH{=}CH_2$$

so that C-1 and C-3 each carry a partial positive charge, and both are attacked by Y. Of course an allylic rearrangement is undetectable in the case of symmetrical allylic carbonium ions, as in the case where R = H, unless isotopic labeling is used. This mechanism has been called the S_N1' mechanism.

However, the carbonium ion cannot always be completely free, since if it were, then, say,

$CH_3CH{=}CHCH_2Cl$ and $CH_3CHClCH{=}CH_2$

14 **15**

should give the same mixture of alcohols when reacting with hydroxide ion, since the carbonium ion from each should be the same. When treated with 0.8 *N* aqueous NaOH at 25°, **14** gave 60% $CH_3CH{=}CHCH_2OH$ and 40% $CH_3CHOHCH{=}CH_2$, while **15** gave these products in yields of 38% and 62%, respectively.[54] This phenomenon is called the *product spread.* In this case, and in most others, the product spread is in the direction of the starting compound. With increasing polarity of solvent, the product spread decreases and in some cases is entirely absent. There is other evidence that the carbonium ion is not completely free. When $H_2C{=}CHCMe_2Cl$ was treated with acetic acid, both acetates were obtained, but also some $ClCH_2CH{=}CMe_2$,[55] and the isomerization was faster than the acetate formation. This could not have arisen from a completely free Cl^- returning to the carbonium ion, since the rate of formation of the rearranged chloride was unaffected by the addition of external Cl^-. All of these facts indicate that the first step of these reactions is formation of an ion pair, which undergoes a considerable amount of internal return.

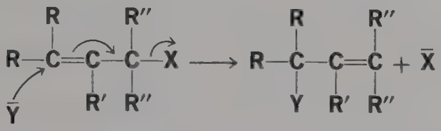
---

[53] For reviews, see DeWolfe and Young, *Chem. Rev.* **56,** 753–901 (1956); Young, *J. Chem. Educ.* **39,** 455–460 (1962); de la Mare in Mayo, "Molecular Rearrangements," vol. 1, pp. 27–110, Interscience Publishers, Inc., New York, 1963; and in Patai, "The Chemistry of Alkenes," Interscience Publishers, Inc., New York, 1964, the sections by Mackenzie, pp. 436–453, and DeWolfe and Young, pp. 681–738.

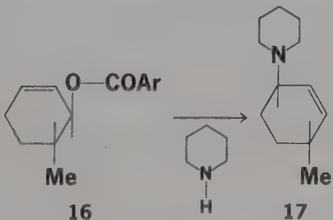
[54] DeWolfe and Young, Ref. 53, give several dozen such examples.

[55] Young, Winstein, and Goering, *J. Am. Chem. Soc.* **73,** 1958 (1951).

Nucleophilic substitution at an allylic carbon may also take place by an S_N2 mechanism, in which case *no allylic rearrangement usually takes place.* However, it is also possible for allylic rearrangements to take place under S_N2 conditions, if the nucleophile attacks at the γ-carbon, rather than at the usual position:

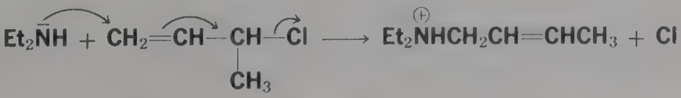


This is called the S_N2' mechanism, and it was predicted theoretically before its actual discovery. It is an allylic shift which is second order; it usually comes about where S_N2 conditions hold, but where α substitution sterically retards the normal S_N2 mechanism. There are thus few well-established cases of the S_N2' mechanism on substrates of the type $C{=}C{-}CH_2X$, while compounds of the form $C{=}C{-}CR_2X$ give the S_N2' rearrangement almost exclusively when they give bimolecular reactions at all.[56] It has been shown that this mechanism is a stereospecific cis process; that is, Y attacks from the same side from which X leaves. This was demonstrated by the finding that *trans*-**16** gave *trans*-**17**, when treated with piperidine:[57]



16 **17**

Evidence for the S_N2' mechanism, in the reaction between diethylamine and 3-chloro-1-butene, was obtained by the principle of successive-labeling-isotope effects.[58] According to this principle, isotope effects should be observed for the molecule successively labeled at each position which undergoes a bond change in going from the reactants to the transition state. If the S_N2' mechanism is correct in this case,



$$Et_2\bar{N}H + CH_2{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}Cl \longrightarrow Et_2\overset{\oplus}{N}HCH_2CH{=}CHCH_3 + Cl$$

---

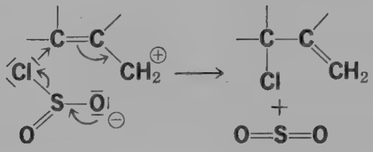
[56] For a discussion of this mechanism, with examples, see DeWolfe and Young, *Chem. Rev.* **56**, 769–784 (1956).

[57] Stork and White, *J. Am. Chem. Soc.* **78**, 4609 (1956).

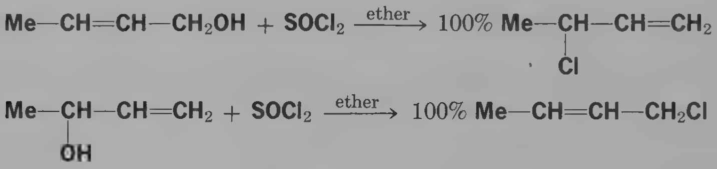
[58] Fry, *Pure Appl. Chem.* **8**, 409 (1964).

then labeling at the nitrogen, the 1-, 2-, and 3-carbons, and the chlorine should all produce isotope effects. The nitrogen isotope effect was not studied, but labeling at the three carbons and at the chlorine produced an isotope effect in each instance.[58]

When a molecule has in an allylic position a leaving group capable of giving the S_Ni reaction, then it is possible for the nucleophile to attack at the γ position instead of the α:



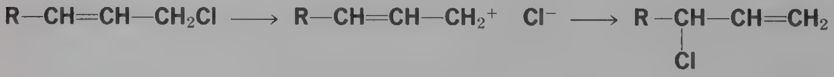
This is called the S_Ni' mechanism and has been demonstrated on 2-buten-1-ol and 3-buten-2-ol:[59]



$$\text{Me—CH=CH—CH}_2\text{OH} + \text{SOCl}_2 \xrightarrow{\text{ether}} 100\%\ \text{Me—}\underset{\text{Cl}}{\underset{|}{\text{CH}}}\text{—CH=CH}_2$$

$$\text{Me—}\underset{\text{OH}}{\underset{|}{\text{CH}}}\text{—CH=CH}_2 + \text{SOCl}_2 \xrightarrow{\text{ether}} 100\%\ \text{Me—CH=CH—CH}_2\text{Cl}$$

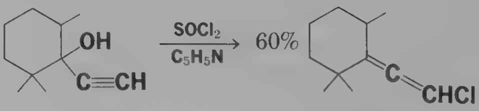
Ordinary allylic rearrangements (S_N1') or S_N2' mechanisms could not be expected to give 100% rearrangement in *both* cases. In the case shown, the nucleophile is only a part of the leaving group, not the whole. But it is also possible to have reactions in which a simple leaving group, such as Cl, comes off to form an ion pair, and then returns, not to the position from whence it came, but to the allylic position:



$$\text{R—CH=CH—CH}_2\text{Cl} \longrightarrow \text{R—CH=CH—CH}_2^+\quad \text{Cl}^- \longrightarrow \text{R—}\underset{\text{Cl}}{\underset{|}{\text{CH}}}\text{—CH=CH}_2$$

Most S_Ni' reactions are of this type.

Allylic rearrangements have also been demonstrated in propargyl systems, for example,[60]

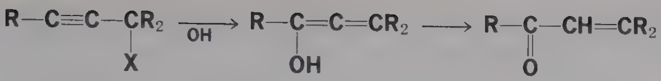


The product in this case is an allene, but such shifts may also give triple-bond compounds, or, if Y = OH, then an enol will be obtained which will tautomerize to an α,β-unsaturated aldehyde or ketone.

---

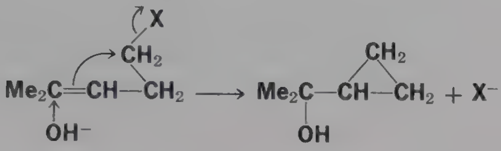
[59] Young, Ref. 53, p. 456. For other examples, see Mark, *Tetrahedron Letters* **1962,** 281; and Pegolotti and Young, *J. Am. Chem. Soc.* **83,** 3251 (1961).

[60] Bhatia, Landor, and Landor, *J. Chem. Soc.* **1959,** 24; Evans, Landor, and Smith, *J. Chem. Soc.* **1963,** 1506.

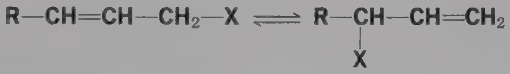


$$R{-}C{\equiv}C{-}\underset{X}{CR_2} \xrightarrow[OH]{} R{-}\underset{OH}{C}{=}C{=}CR_2 \longrightarrow R{-}\underset{O}{\overset{}{C}}{-}CH{=}CR_2$$

An unusual type of "allylic" shift has been shown to occur in a homoallylic system, where a cyclopropyl ring was formed, presumably by an S_N2' type of mechanism.[61]

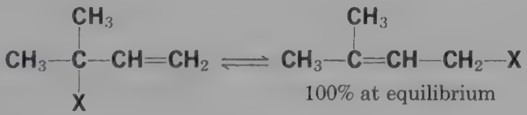


An allylic rearrangement in which the nucleophile is the same as the leaving group is an isomerization.[62]



$$R{-}CH{=}CH{-}CH_2{-}X \rightleftharpoons R{-}\underset{X}{CH}{-}CH{=}CH_2$$

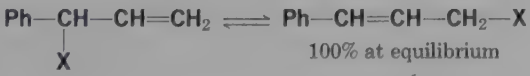
This type of isomerization may proceed by any of the three mechanisms mentioned: S_N1', S_N2', or, as we have seen, S_Ni'. Examples are known where X = halide, OCOR, and OH (actually OH_2^+, the protonated OH group). It is of interest to examine the question of the direction of such isomerizations. When the reaction is permitted to proceed to equilibrium, the product will be thermodynamically controlled: the isomer of lower energy will predominate. Olefin stability increases with increasing alkyl substitution, so that where only alkyl groups are involved, the more stable isomer will have the X on the less highly substituted carbon, e.g.,[63]



$$CH_3{-}\underset{X}{\overset{CH_3}{C}}{-}CH{=}CH_2 \rightleftharpoons CH_3{-}\overset{CH_3}{C}{=}CH{-}CH_2{-}X$$

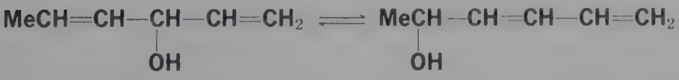
100% at equilibrium

If the double bond in one isomer can be in conjugation with an aromatic ring, a triple bond, another double bond, or a carbonyl group, then that isomer is more stable and will predominate at equilibrium, e.g.,[64]



$$Ph{-}\underset{X}{CH}{-}CH{=}CH_2 \rightleftharpoons Ph{-}CH{=}CH{-}CH_2{-}X$$

100% at equilibrium



$$MeCH{=}CH{-}\underset{OH}{CH}{-}CH{=}CH_2 \rightleftharpoons \underset{OH}{MeCH}{-}CH{=}CH{-}CH{=}CH_2$$

100% at equilibrium

---

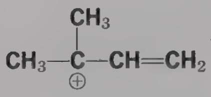
[61] Hanack and Görler, *Chem. Ber.* **96**, 2121 (1963).

[62] For a review, see Braude, *Quart. Rev.* (*London*) **4**, 404–425 (1950).

[63] Claisen, *J. prakt. Chem.* **105**, 65 (1922).

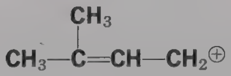
[64] Pocker, *J. Chem. Soc.* **1958**, 4318; Braude and Timmons, *J. Chem. Soc.* **1950**, 2000, 2007.

It might be expected from this that, say, in an S_N1' reaction of $Me_2C{=}CHCH_2Cl$ with water, the predominant product would be the unrearranged $Me_2C{=}CHCH_2OH$ with only a smaller amount of the rearranged $Me_2COHCH{=}CH_2$. However, the main product here (85%) is the tertiary alcohol, although thermodynamically it is the less stable isomer. Equilibrium is not reached, and the product is kinetically controlled (see p. 204). In S_N1' reactions the thermodynamically less stable product is almost always formed in greater than the equilibrium proportion, because the relative rates of the two reactions are determined by the relative magnitudes of the positive charges on the two carbons. For example, in the case mentioned,



$CH_3-\underset{\oplus}{\overset{CH_3}{\overset{|}{C}}}-CH{=}CH_2$

A



$CH_3-\overset{CH_3}{\overset{|}{C}}{=}CH-CH_2^{\oplus}$

B

A contributes more to the resonance hybrid than does **B** (because tertiary carbons are more stable than primary) so that the charge on the tertiary carbon is greater than that on the primary carbon. However, whether one isomer or the other will predominate is usually not easy to predict in a given case. The solvent exerts a great effect. For example, the substrate mentioned gave 85% of the tertiary product when water was the solvent, but only 45% in acetic acid containing silver acetate. Increasing solvent polarity favors the formation of product resulting from attack at the more positive carbon. The existence of the product spread further complicates the picture.

Nucleophilic Substitution at an Aliphatic Trigonal Carbon.[65] **The Tetrahedral Mechanism.** All the mechanisms so far discussed take place at a saturated carbon atom. Nucleophilic substitutions are also important at trigonal carbons, especially when the carbon is double-bonded to an oxygen, a sulfur, or a nitrogen. Nucleophilic substitution at vinyl carbons is considered in the next section; at aromatic carbons in Chapter 13.

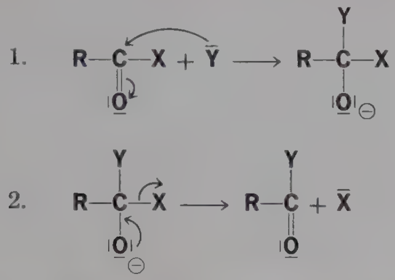
At a carbonyl group (or the corresponding nitrogen and sulfur analogs) substitution most often proceeds by a second-order mechanism, which in this book will be called the *tetrahedral mechanism*.[66] S_N1 mechanisms, involving carbonium ions, are sometimes found with these substrates, especially with essentially ionic compounds such as $RCO^+ \;\; BF_4^-$, but the tetrahedral mechanism is far more prevalent. Although this mechanism displays second-order kinetics, it is not the same as the S_N2 mechanism previously discussed. Simple S_N2 mechanisms have rarely been demonstrated for carbonyl substrates.[67] In the tetrahedral mechanism, first Y attacks to give an intermediate containing both X and Y, and then X leaves. This sequence, impossible at a saturated carbon, is possible at an unsaturated one, because the central carbon can release a pair of electrons to the oxygen and so preserve its octet:

---

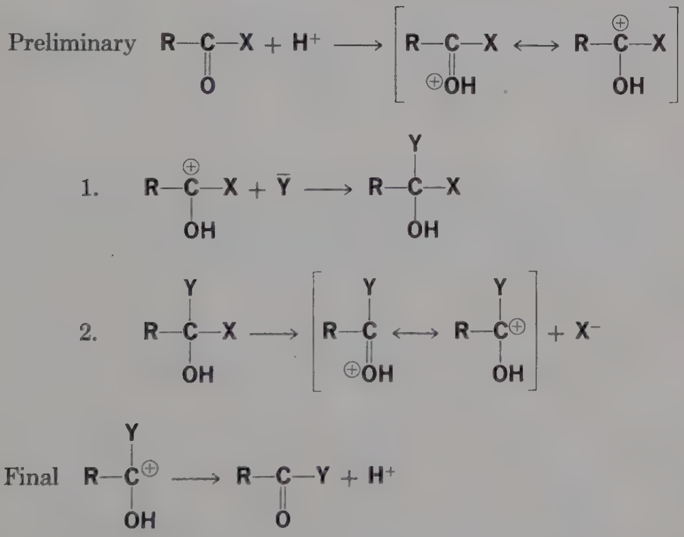
[65] For a review, see Satchell, *Quart. Rev.* (*London*) **17**, 160–203 (1963).

[66] For a review of this mechanism, see Bender, *Chem. Rev.* **60**, 53–113 (1960).

[67] For an example of a simple S_N2 mechanism at a carbonyl substrate (the reaction between phenols and chloroacetyl chloride), see Briody and Satchell, *J. Chem. Soc.* **1965**, 168.



When reactions are carried out in acid solution, there may be in addition a preliminary and a final step:



The hydrogen ion is a catalyst. The reaction rate is increased because it is easier for the nucleophile to attack the carbon when the electron density of the latter has been decreased.

Evidence for the existence of the tetrahedral mechanism is as follows:

1. The kinetics are first order each in the substrate and in the nucleophile, as predicted by the mechanism.

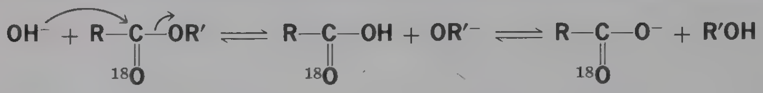
2. There is other kinetic evidence in accord with a tetrahedral intermediate. For example, the rate "constant" for the reaction between acetamide and hydroxylamine is not constant but decreases with increasing hydroxylamine concentration.[68] This is not a smooth decrease; there is a break

---

[68] Jencks and Gilchrist, *J. Am. Chem. Soc.* **86**, 5616 (1964).

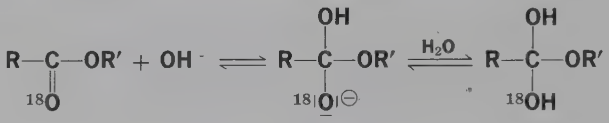
in the curve. A straight line is followed at low hydroxylamine concentration and another straight line at high concentration. This means that the identity of the rate-determining step is changing. Obviously, this cannot happen if there is only one step: there must be two steps, and hence an intermediate. Similar kinetic behavior has been found in other cases as well;[69] in particular, plots of rate against pH are often bell-shaped.

3. Basic hydrolysis has been carried out on esters labeled with ^{18}O in the carbonyl group.[70] If this reaction proceeded by the normal S_N2 mechanism, then all of the ^{18}O would remain in the carbonyl group, even if, in an equilibrium process, some of the acid formed went back to the starting material:



$$\mathrm{OH^- + R{-}\underset{\overset{\|}{^{18}O}}{C}{-}OR' \rightleftharpoons R{-}\underset{\overset{\|}{^{18}O}}{C}{-}OH + OR'^- \rightleftharpoons R{-}\underset{\overset{\|}{^{18}O}}{C}{-}O^- + R'OH}$$

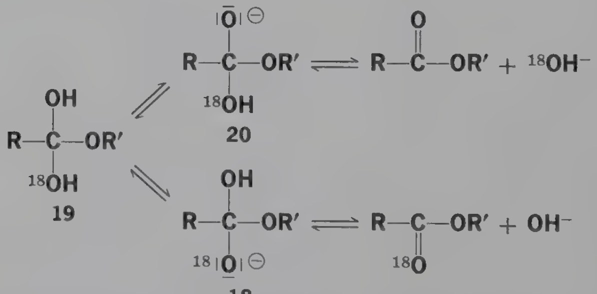
On the other hand, if the tetrahedral mechanism is operating,



$$\mathrm{R{-}\underset{\overset{\|}{^{18}O}}{C}{-}OR' + OH^- \rightleftharpoons R{-}\underset{\overset{|}{^{18}O^-}}{\overset{\overset{OH}{|}}{C}}{-}OR' \xrightleftharpoons{H_2O} R{-}\underset{\overset{|}{^{18}OH}}{\overset{\overset{OH}{|}}{C}}{-}OR'}$$

18 **19**

then the intermediate **18**, by picking up a proton, becomes converted to the symmetrical intermediate **19**. In this intermediate the OH groups are equivalent, and (except for the small $^{18}O/^{16}O$ isotope effect) either one can lose a proton with equal facility:



20

19

18

The intermediates **18** and **20** can now lose OR′ to give the acid (not shown in the equations given), or they may lose OH to regenerate the ester. If **18** goes back to ester, the ester will still be labeled, but if **20** reverts to ester, the ^{18}O will be lost. A test of the two possible mechanisms then is to stop the reaction before completion and to analyze the recovered ester for ^{18}O.

---

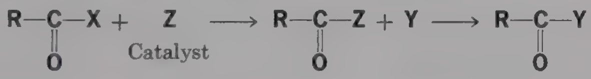
[69] Hand and Jencks, *J. Am. Chem. Soc.* **84**, 3505 (1962); Bruice and Fedor, *J. Am. Chem. Soc.* **86**, 4886 (1964); Johnson, *J. Am. Chem. Soc.* **86**, 3819 (1964); Fedor and Bruice, *J. Am. Chem. Soc.* **86**, 5697 (1964), **87**, 4138 (1965); Kevill and Johnson, *J. Am. Chem. Soc.* **87**, 928 (1965); Leinhard and Jencks, *J. Am. Chem. Soc.* **87**, 3855 (1965); and Schowen, Jayaraman, and Kershner, *J. Am. Chem. Soc.* **88**, 3373 (1966).

[70] Bender, *J. Am. Chem. Soc.* **73**, 1626 (1951); Bender and Thomas, *J. Am. Chem. Soc.* **83**, 4183 (1961).

This is just what was done by Bender, who found that the ester had lost ^{18}O. A similar experiment carried out for acid-catalyzed hydrolysis of ethyl benzoate showed that here too the ester lost ^{18}O. However, alkaline hydrolysis of substituted benzyl benzoates showed *no* ^{18}O loss.[71] This result does not necessarily mean that no tetrahedral intermediate is involved in this case. If **18** and **20** do not revert to ester, but go entirely to acid, then no ^{18}O loss will be found even with a tetrahedral intermediate. In the case of benzyl benzoates this may very well be happening, because formation of the acid relieves steric strain. Even the experiments which *do* show ^{18}O loss do not *prove* the existence of the tetrahedral intermediate, though they make it very likely. It is possible that ^{18}O is lost by some independent process, not leading to ester hydrolysis.

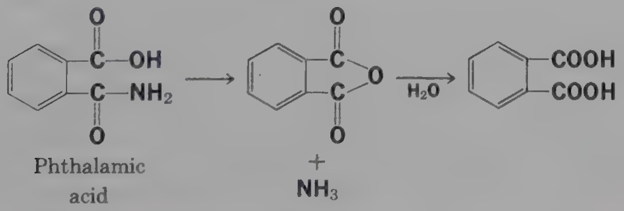
4. In a few cases, tetrahedral intermediates have been isolated[72] or detected spectrally.

Some nucleophilic substitutions at a carbonyl carbon are *catalyzed* by nucleophiles. There occur, in effect, two tetrahedral mechanisms:

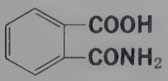


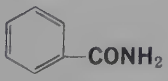
$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}X} + \underset{\text{Catalyst}}{\mathrm{Z}} \longrightarrow \mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}Z} + \mathrm{Y} \longrightarrow \mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}Y}$$

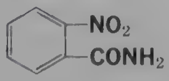
For an example, see page 309. When this happens internally, we have an example of a neighboring-group mechanism at a carbonyl carbon. For example, the hydrolysis of phthalamic acid takes place as follows:

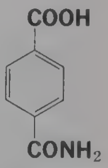


Evidence comes from comparative rate studies.[73] Thus phthalamic acid was hydrolyzed about 10^5 times faster than benzamide ($PhCONH_2$) at about the same concentration of hydrogen ions. That this enhancement of rate was not caused by the inductive or resonance effects of COOH (an electron-withdrawing group) was shown by the fact that both *o*-nitrobenzamide and terephthalamic acid were hydrolyzed more slowly than benzamide:









Rate ratio: 10^5 1 0.1 Less than 1

---

[71] Bender, Matsui, Thomas, and Tobey, *J. Am. Chem. Soc.* **83**, 4193 (1961).

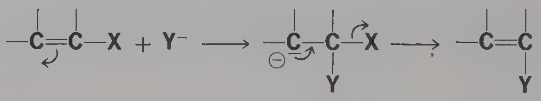
[72] Ref. 66, pp. 58–59.

[73] Bender, Chow, and Chloupek, *J. Am. Chem. Soc.* **80**, 5380 (1958).

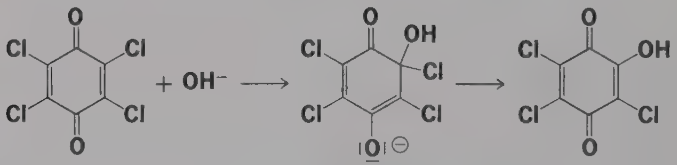
Many other examples of neighboring-group participation at a carbonyl carbon have been reported.[74] It is likely that nucleophilic catalysis is involved in enzyme catalysis of ester hydrolysis.

The attack of a nucleophile on a carbonyl group may result in substitution or addition (Chapter 16), though the first step of each mechanism is the same. The principal factor which determines the product is the identity of the group X in RCOX. When X is alkyl or hydrogen, addition usually takes place. When X is halogen, OH, OCOR, NH_2, etc., the usual reaction is substitution.

Nucleophilic Substitution at a Vinyl Carbon.[75] Nucleophilic substitution at a vinyl carbon is difficult (see p. 282), but examples are known. In a few cases the S_N1 mechanism has been shown, and in other cases the tetrahedral mechanism. The latter takes place with much less facility than with carbonyl groups, since the negative charge of the intermediate must be borne by a carbon, which is less electronegative than oxygen, sulfur, or nitrogen:



Such an intermediate can also stabilize itself by combining with a positive species, and when it does, the reaction is nucleophilic addition to a C=C double bond (see Chapter 15). It is not surprising that with vinyl substrates, addition and substitution often compete. For chloroquinones, where the charge is spread by resonance, tetrahedral intermediates have been isolated:[76]



Isolated

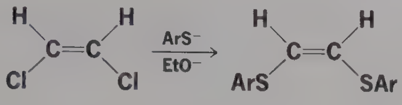
Two other mechanisms have been demonstrated for vinyl substrates. One involves an *elimination-addition* sequence, and the other *addition-elimination*. The elimination-addition sequence has also been shown for aromatic substrates (see p. 492). An example of a reaction involving this mechanism is the substitution of ArS for the chlorine of *cis*-1,2-dichloroethylene:

---

[74] For examples, see Bruice and Pandit, *J. Am. Chem. Soc.* **82,** 5858 (1960); Newman and Hishida, *J. Am. Chem. Soc.* **84,** 3582 (1962); Kupchan and Saettone, *Tetrahedron* **18,** 1403 (1962); Bender, Reinstein, Silver, and Mikulak, *J. Am. Chem. Soc.* **87,** 4545 (1965); and Zimmering, Westhead, and Morawetz, *Biochim. Biophys. Acta* **25,** 376 (1957).

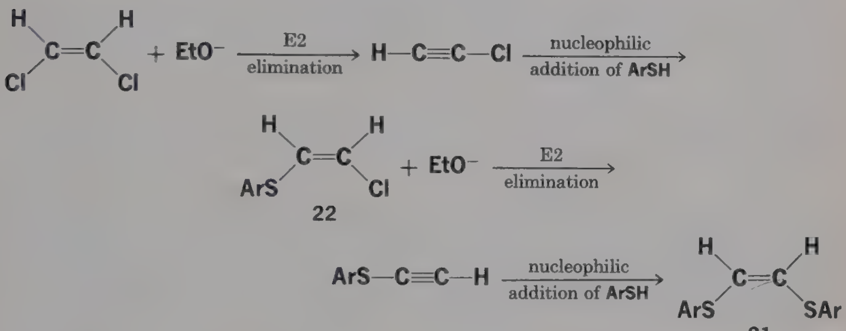
[75] For a review, see Patai and Rappoport, in Patai, "The Chemistry of Alkenes," pp. 525–546, Interscience Publishers, Inc., New York, 1964. The nomenclature in this reference differs from that used in the present book. Patai and Rappoport use the term "addition-elimination" to refer to three mechanisms: those we call tetrahedral, S_N2, and addition-elimination.

[76] Hancock, Morrell, and Rhom, *Tetrahedron Letters* **1962,** 987.



21

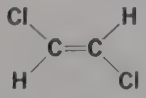
The mechanism may be formulated as



22

21

In the first step ethoxide ion causes E2 elimination (p. 728) to produce chloroacetylene. The E2 mechanism is stereoselective and proceeds rapidly when the hydrogen and halogen are trans, as they are in this case. In the second step the thiol adds to the acetylene by a nucleophilic addition mechanism (p. 567) to give **22.** This reaction is also stereoselective, with ArS and H adding from opposite sides (trans addition). Thus **22** still has a hydrogen trans to a halogen, and the two steps are repeated to give the cis product **(21).** Evidence for this sequence[77] is as follows: (1) the reaction does not proceed without ethoxide ion, and the rate is dependent on this ion, and not on ArS⁻. (2) *trans*-1,2-Dichloroethylene:

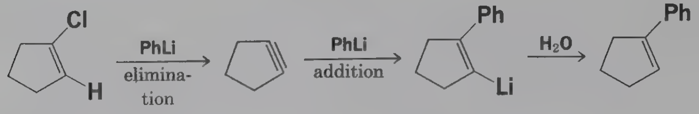


does not react under these conditions. There is no hydrogen trans to either chlorine, so that the rate of an E2 reaction is greatly reduced. (3) Under the same reaction conditions, chloroacetylene gave **22** and **21**; and (4) **22** treated with ArS⁻ gave no reaction, but when EtO⁻ was added, **21** was obtained.

It is interesting that the elimination-addition mechanism has even been shown to occur in five- and six-membered *cyclic* systems, where triple bonds are greatly strained. Thus treatment of 1-chlorocyclopentene with phenyllithium proceeds as follows:[78]

---

[77] Truce, Boudakian, Heine, and McManimie, *J. Am. Chem. Soc.* **78**, 2743 (1956); Flynn, Badiger, and Truce, *J. Org. Chem.* **28**, 2298 (1963).



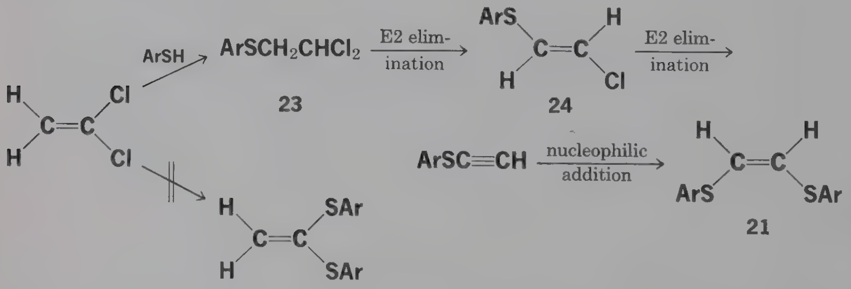
Evidence for this mechanism was obtained by radioactive labeling, similar to that used for the benzyne mechanism (p. 492).

The elimination-addition sequence has also been demonstrated for certain reactions of saturated substrates, for example, $ArSO_2CH_2CH_2SO_2Ar$.[79] Treatment of this with ethoxide proceeds as follows:

$$ArSO_2CH_2CH_2SO_2Ar \xrightarrow[\text{E2 elimination}]{EtO^-} ArSO_2CH{=}CH_2 \xrightarrow[\text{addition}]{EtO^-} ArSO_2CH_2CH_2OEt$$

Mannich bases (see reaction **6-17**) of the type $RCOCH_2CH_2NR_2$ similarly undergo nucleophilic substitution by the elimination-addition mechanism. The nucleophile replaces the NR_2 group.

The addition-elimination sequence is of course impossible for saturated substrates. It has been demonstrated for the reaction between 1,1-dichloroethylene and ArS^-, catalyzed by EtO^-.[80] The product was not the 1,1-dithiophenoxy compound, but was **21**. Isolation of **23** and **24** showed that an addition-elimination mechanism was taking place:



23

24

21

In this case the trans compound **24** gave elimination (though slowly) because strong conditions were used. Both of these mechanisms lead to overall retention of configuration, since in each case both addition and elimination are trans.

The simple S_N2 mechanism has never been demonstrated for vinyl substrates.

---

[78] Montgomery, Scardiglia, and Roberts, *J. Am. Chem. Soc.* **87**, 1917 (1965); Montgomery and Applegate, *J. Am. Chem. Soc.* **89**, 2952 (1967).

[79] Kader and Stirling, *J. Chem. Soc.* **1962**, 3686.

[80] Truce and Boudakian, *J. Am. Chem. Soc.* **78**, 2748 (1956).

TABLE 1. Average relative S_N2 rates for some alkyl substrates[81]

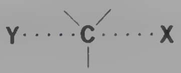
R	*Relative rate*
Methyl	30
Ethyl	1
Propyl	0.4
Butyl	0.4
Isopropyl	0.025
Isobutyl	0.03
Neopentyl	10^{-5}
Allyl	40
Benzyl	120

REACTIVITY

A great deal of work has been done on this subject. Many small effects have been examined. However, much is still poorly understood, and the results are often anomalous and hard to explain. In this section only approximate generalizations will be attempted.

The Effect of Substrate Structure. The effect on the reactivity of a change in substrate structure depends on the mechanism.

1. *Branching at the α- and β-carbons.* For the S_N2 mechanism, branching at either the α- or the β-carbon decreases the rate. Tertiary systems seldom react by the S_N2 mechanism, and neopentyl systems react very slowly. Table 1 shows average relative rates for some alkyl substrates.[81] The reason for these low rates is almost certainly steric.[82] The transition state **1** is more crowded when larger groups are close to the central carbon. It was pointed out on page 271 that allylic substrates undergo S_N2' reactions only when there is branching at the α position. Ordinary S_N2 reactions are so slowed by this α branching that the nucleophile attacks the allylic position. The tetrahedral mechanism for substitution at a carbonyl carbon is also slowed or blocked completely by α or β branching, for similar reasons.



1

For the S_N1 mechanism, α branching increases the rate, as shown in Table 2. We may explain this by the stability order of carbonium ions (tertiary > secondary > primary) and by the inductive effect of three alkyl groups, which increases the electron density on the central carbon and makes it

---

[81] This table is from Streitwieser, Ref. 1, p. 13. Also see Table 2, Chapter 9 (p. 233).

[82] For a review on this point, see Ingold, *Quart. Rev.* (*London*) **11**, 1–14 (1957).

TABLE 2. Relative rates of solvolysis of RBr in two solvents[83]

RBr *substrate*	*In 60% ethanol at 55°*	*In water at 50°*
MeBr	2.08	1.05
EtBr	1.00	1.00
iso-**PrBr**	1.78	11.6
tert-**BuBr**	2.41×10^4	1.2×10^6

easier for a negative group to cleave. For simple alkyl groups, the S_N1 mechanism is important under all conditions only for tertiary substrates. As previously indicated by the work of Weiner and Sneen (p. 262) and of Streitwieser and coworkers (p. 262), secondary substrates generally react by the S_N2 mechanism, except that the S_N1 mechanism may become important at high solvent polarities. Table 2 shows that isopropyl bromide reacts less than twice as fast as ethyl bromide in the relatively nonpolar 60% ethanol (compare this with the 10^4 ratio for *tert*-butyl bromide, where the mechanism is certainly S_N1), but in the more polar water the rate ratio is 11.6. For some tertiary substrates, the rate of S_N1 reaction is greatly increased by the relief of B-strain in the formation of the carbonium ion (see p. 234). Except where B-strain is involved, β branching has little effect on the S_N1 mechanism, except that carbonium ions with β branching undergo rearrangements readily. Of course, isobutyl and neopentyl are primary substrates, and for this reason react very slowly by the S_N1 mechanism, but not more slowly than the corresponding ethyl or propyl compounds.

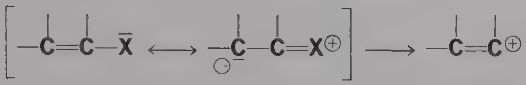
To sum up, primary and secondary substrates generally react by the S_N2 mechanism, and tertiary by the S_N1 mechanism. However, tertiary substrates seldom undergo nucleophilic substitution at all. Elimination is always a possible side reaction of nucleophilic substitutions (wherever a β hydrogen is present), and with tertiary substrates it usually predominates. With a few exceptions, nucleophilic substitutions at a tertiary carbon have little or no preparative value.

2. *Unsaturation at the α-carbon.* Vinyl, acetylenic, and aryl substrates are very unreactive toward nucleophilic substitutions. For these systems both the S_N1 and S_N2 mechanisms are greatly slowed or stopped altogether. This may be attributed to several factors. The first of these is that sp^2 (and even more, sp) carbons have a higher electronegativity than sp^3 carbons and thus have a greater attraction for the electrons of the bond. As we have seen (p. 229), an sp—H bond has a higher acidity than an sp^3—H bond, with an sp^2—H bond in between. This is reasonable: the carbon retains the electrons when the proton is lost, and an sp carbon, which has the greatest hold on the electrons, loses the proton most easily. But in a nucleophilic substitution, the leaving group *carries off* the electron pair, so that the situation is reversed, and it is the sp^3 carbon which loses the leaving group and the elec-

---

[83] These values are from Streitwieser, Ref. 1, p. 43, where values are also given for other conditions. Methyl bromide reacts faster than ethyl bromide (and in the case of 60% ethanol, isopropyl bromide) because some of it (probably most of it) is reacting by the S_N2 mechanism.

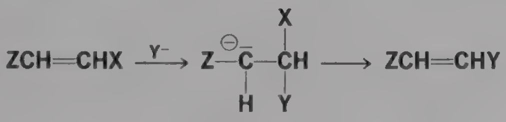
tron pair most easily. Another factor holds only where the leaving group has one or more unshared pairs (of course, most of them do) and applies only to S_N1 reactions. When X has an unshared pair, the *molecule* is stabilized by resonance in which some of the electron density of the leaving group is transferred into the C—X bond, greatly strengthening it:



$$\left[-\overset{|}{C}=\overset{|}{C}-\bar{X} \longleftrightarrow -\underset{\ominus}{\overset{|}{\underline{C}}}-\overset{|}{C}=X^{\oplus}\right] \longrightarrow -\overset{|}{C}=\overset{|}{C}^{\oplus}$$

This resonance is lost on going to the carbonium ion, and there is no resonance there for a compensating gain. It may be recalled (p. 23) that bond distances decrease with increasing *s* character. Thus the bond length for a vinyl or aryl C—Cl bond is 1.73 Å, as compared to 1.78 Å for a saturated C—Cl bond. Other things being equal, a shorter bond is a stronger bond.

Nucleophilic substitution may often be carried out on substrates of the type ZCH=CHX, where Z is an electron-withdrawing group such as HCO, RCO, EtOOC, $ArSO_2$, NC, etc. In these cases the mechanism is the tetrahedral one (p. 274), and the Z serves to stabilize the carbanion:



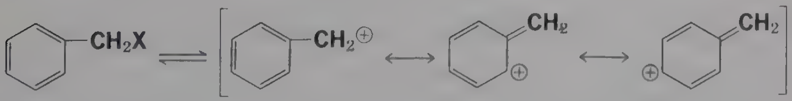
$$ZCH{=}CHX \xrightarrow{Y^-} Z-\underset{H}{\overset{\ominus}{\underline{C}}}-\underset{Y}{\overset{X}{C}}H \longrightarrow ZCH{=}CHY$$

In addition, reactions at vinyl substrates may in certain cases proceed by the elimination-addition or addition-elimination mechanisms (p. 278).

In contrast to such systems, substrates of the type RCOX are usually much more reactive than the corresponding RCH_2X, but the mechanism with these substrates is almost always the tetrahedral mechanism. For reactivity in aryl systems, see Chapter 13.

3. *Unsaturation at the β-carbon.* S_N1 rates are greatly increased when there is a double bond in the β position, so that allylic and benzylic substrates react rapidly (Table 3). This is because the carbonium ion is stabilized by resonance:

$$CH_2{=}CH{-}CH_2{-}X \rightleftharpoons \left[CH_2{=}CH{-}CH_2^{\oplus} \longleftrightarrow \overset{\oplus}{C}H_2{-}CH{=}CH_2\right]$$



In sharp contrast to the case of α unsaturation, where there was resonance stabilization of the molecule but not of the ion, here there is resonance stabilization of the ion, but not of the molecule, since in the molecule the X group and the unsaturation are too far apart for resonance interaction. As shown in Table 3, a second and a third phenyl group increase the rate still

TABLE 3. Relative rates for the S_N1 reaction between ROTs and ethanol at 25°[84]

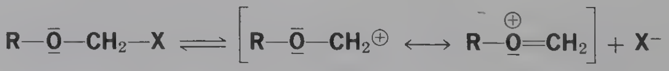
Group	*Relative rate*
Et	0.26
iso-Pr	0.69
$CH_2{=}CHCH_2$	8.6
$PhCH_2$	100
Ph_2CH	$\sim 10^5$
Ph_3C	$\sim 10^{10}$

more, because these carbonium ions are more stable yet. It should be remembered that, with allylic systems, allylic rearrangements are possible.

In general, S_N1 rates at an allylic substrate are increased by any substituent in the 1- or 3-position which can stabilize the carbonium ion by resonance or hyperconjugation.[85] Among these are alkyl, aryl, and halo groups.

S_N2 rates for allylic and benzylic systems are also increased (see Table 1), probably owing to resonance possibilities in the transition state. Triple bonds in the β position (in propargyl systems) have about the same effect as double bonds.[86] Alkyl, aryl, halo, and cyano groups, among others, in the 3-position of allylic substrates increase S_N2 rates, owing to increased resonance in the transition state, but alkyl and halo groups in the 1-position decrease the rates, because of steric hindrance.

4. *α substitution.* Compounds of the formula ZCH_2X, where $Z = RO$,[87] RS, or R_2N, undergo S_N1 reactions very rapidly, because of the increased resonance in the carbonium ion. These groups have an unshared pair on an atom directly attached to the positive carbon, and this greatly stabilizes the carbonium ion:



$$R{-}\overline{\underline{O}}{-}CH_2{-}X \rightleftharpoons \left[R{-}\overline{\underline{O}}{-}CH_2^{\oplus} \longleftrightarrow R{-}\overset{\oplus}{\underline{O}}{=}CH_2\right] + X^-$$

The inductive effects of these groups would be expected to decrease S_N1 rates (see section 6, p. 285), so that the resonance effect is far more important.

When Z in ZCH_2X is RCO, HCO, ROCO, NH_2CO, or NC, S_N1 rates are decreased compared to CH_3X, presumably owing to the electron-withdrawing effects of these groups. However, the presence in the α position of one of these groups *increases* S_N2 rates. One reason suggested for this is that the attacking nucleophile can overlap with the π orbital on the group Z at the same time that it is overlapping with the central carbon, e.g.,

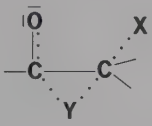
---

[84] Streitwieser, Ref. 1, p. 75. Actually, the figures for Ph_2CHOTs and Ph_3COTs are estimated from the general reactivity of these substrates. Solvolysis rates in ethanol have not been measured for these compounds.

[85] For discussions of the relative reactivities of different allylic substrates, see de la Mare, in Mayo, "Molecular Rearrangements," vol. 1, pp. 42–47, 58–62, Interscience Publishers, Inc., New York, 1963; and DeWolfe and Young, in Patai, "The Chemistry of Alkenes," pp. 683–688, 695–697, Interscience Publishers, Inc., New York, 1964.

[86] Hatch and Chiola, *J. Am. Chem. Soc.* **73**, 360 (1951); Jacobs and Brill, *J. Am. Chem. Soc.* **75**, 1314 (1953).

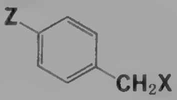
[87] For a review of the reactions of α-halo ethers, see Summers, *Chem. Rev.* **55**, 301–353 (1955), pp. 319–333.



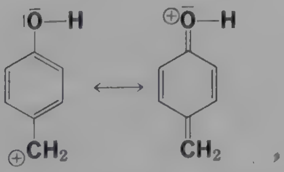
This would stabilize the transition state. Evidence for this view is that replacement of an α hydrogen by R_3Si[88] or RHg,[89] where overlapping can also occur, also greatly increases the rate.

5. *β substitution.* For compounds of the type ZCH_2CH_2X, where Z is any of the groups listed in the previous section as well as halogen or phenyl, S_N1 rates are lower than for unsubstituted systems, because the resonance effects mentioned in section 4 are absent, but the inductive effects are still there, though smaller. These groups in the β position do not have much effect on S_N2 rates, unless they behave as neighboring groups and enhance the rate through anchimeric assistance.

6. *The effect of electron-donating and -withdrawing groups.* If substitution rates of a series of compounds



are measured, it is possible to study the electronic effects of groups Z on the reaction. Steric effects of Z are minimized or eliminated because Z is so far from the reaction site. For S_N1 reactions electron-withdrawing Z decrease the rate and electron-donating Z increase it, because the latter decrease the energy of the transition state (and of the carbonium ion) by spreading the positive charge, e.g.,



while electron-withdrawing groups increase the charge. The Hammett σ-ρ relationship (see p. 239) correlates fairly successfully the rates of many of these reactions (with σ^+ instead of σ). ρ values are generally about -4, which is to be expected for a reaction where a positive charge is created in the transition state.

---

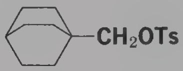
[88] Eaborn and Jeffrey, *J. Chem. Soc.* **1954**, 4266.

[89] Ledwith and Phillips, *J. Chem. Soc.* **1962**, 3796.

For S_N2 reactions no such simple correlations are found.[90] In this mechanism bond breaking is about as important as bond making in the rate-determining step, and substituents have an effect on both steps, often in opposite directions.

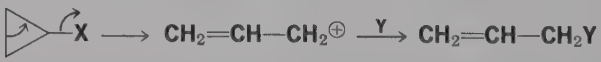
For Z = alkyl, the Baker-Nathan order (p. 57) is usually observed, both for S_N1 and S_N2 reactions.

In para-substituted benzyl systems, steric effects have been removed, but inductive and resonance effects are still present. However, Holtz and Stock have been able to study a system which removes not only steric effects, but also resonance effects. This is the 4-substituted bicyclo[2.2.2]octylmethyl tosylate system:[91]



In this system steric effects are completely absent, owing to the rigidity of the molecules, and only inductive effects operate.[92] By this means Holtz and Stock showed that electron-withdrawing groups increase the rate of S_N2 reactions. This may be ascribed to a stabilization of the transition state by withdrawal of some of the electron density.

7. *Cyclic substrates.* When the leaving group is on a ring, I-strain may play a part. In Chapter 9 (p. 235) it was shown that S_N1 rates of cyclopropyl and cyclobutyl halides are less than those for larger rings, a result attributed to I-strain. A similar situation holds for S_N2 reactions, since here too the central carbon must achieve planarity or near-planarity in the transition state. For larger rings, eclipsing effects are relieved in the conversion of a tetrahedral to a trigonal carbon (in S_N1 reactions), and thus compounds with rings of five and of seven to eleven members react faster than those in which the leaving group is on a six-membered ring, where such effects are absent (Table 4, Chapter 9, p. 235). Solvolysis of cyclopropyl substrates generally leads to ring opening.[93]



8. *Bridgeheads.* Nucleophilic substitutions at bridgeheads are impossible or very slow (see pp. 254 and 258).

9. *Deuterium substitution.* α and β secondary isotope effects affect the rate in various ways (see p. 215).

10. *Electronic effects on the tetrahedral mechanism.* For substrates which react by the tetrahedral mechanism, electron-withdrawing groups increase the rate, and electron-donating groups decrease it.

---

[90] See Sugden and Willis, *J. Chem. Soc.* **1951**, 1360; Baker and Nathan, *J. Chem. Soc.* **1935**, 840.

[91] Holtz and Stock, *J. Am. Chem. Soc.* **87**, 2404 (1965).

[92] It should be recalled (p. 19) that this includes effects transmitted both along the chains and through space (field effects).

[93] See, for example, DePuy, Schnack, Hausser, and Wiedemann, *J. Am. Chem. Soc.* **87**, 4006 (1965).

TABLE 4. List of groups in approximately descending order of reactivity toward S_N1 and S_N2 reactions
Z is RCO, HCO, ROCO, NH_2CO, NC, or similar groups

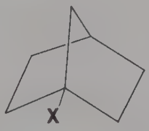
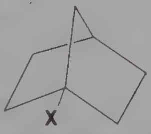
S_N1 reactivity	*S_N2 reactivity*
Ar_3CX	Ar_3CX
Ar_2CHX	Ar_2CHX
$ROCH_2X$, $RSCH_2X$, R_2NCH_2X	$ArCH_2X$
R_3CX	ZCH_2X
$ArCH_2X$	$-\overset{\vert}{C}=\overset{\vert}{C}CH_2X$
$-\overset{\vert}{C}=\overset{\vert}{C}CH_2X$	$RCH_2X \approx RCHDX \approx RCHDCH_2X$
R_2CHX	R_2CHX
$RCH_2X \approx R_3CCH_2X$	R_3CX
$RCHDX$	ZCH_2CH_2X
$RCHDCH_2X$	R_3CCH_2X
ZCH_2X	$-\overset{\vert}{C}=\overset{\vert}{C}X$
ZCH_2CH_2X	ArX
$-\overset{\vert}{C}=\overset{\vert}{C}X$	
ArX	
	

Table 4 is an approximate listing of groups in order of S_N1 and S_N2 reactivity.

The Effect of the Attacking Nucleophile.[94] Any species which has an unshared pair (i.e., any Lewis base) may be a nucleophile, whether it is neutral or has a negative charge. The rates of S_N1 reactions are independent of the identity of the nucleophile, since it does not appear in the rate-determining step. This may be illustrated by the effect of changing the nucleophile from H_2O to OH^- for a primary and a tertiary substrate. For methyl bromide, which reacts by an S_N2 mechanism, the rate is multiplied by more than 5000 by the change to the more powerful nucleophile OH^-, but for *tert*-butyl bromide, which reacts by an S_N1 mechanism, the rate is unaffected.[95]

For S_N2 reactions there are four main principles which govern the effect of the nucleophile on the rate, though the nucleophilicity order is not invariant, but depends on substrate, solvent, leaving group, etc.

---

[94] For reviews, see Bunnett, *Ann. Rev. Phys. Chem.* **14**, 271–290 (1963); and Edwards and Pearson, *J. Am. Chem. Soc.* **84**, 26 (1962).

[95] Bateman, Cooper, Hughes, and Ingold, *J. Chem. Soc.* **1940**, 925.

1. A nucleophile with a negative charge is always a more powerful nucleophile than its conjugate acid (assuming the latter is also a nucleophile). Thus OH^- is more powerful than H_2O; NH_2^- than NH_3, etc. See the example given above.

2. In comparing nucleophiles whose attacking atom is within the same row of the periodic table, nucleophilicity is roughly in order of basicity, though basicity is thermodynamically controlled and nucleophilicity is kinetically controlled. So an approximate order of nucleophilicity is $NH_2^- > RO^- > OH^- > R_2NH > ArO^- > NH_3 >$ pyridine $> F^- > H_2O > ClO_4^-$, and another is $R_3C^- > R_2N^- > RO^- > F^-$ (see Table 1 in Chapter 8, p. 219). This type of correlation works best when the structures of the nucleophiles being compared are similar, as with a set of substituted phenoxides.

3. Going down the periodic table, nucleophilicity increases, though basicity is decreasing. Thus the usual order of halide nucleophilicity is $I^- > Br^- > Cl^- > F^-$ (though as we shall see below, this order is solvent-dependent). Similarly, any sulfur nucleophile is more powerful than its oxygen analog, and the same for phosphorus versus nitrogen. There have been several explanations offered for this distinction between basicity and nucleophilic power. One of these is that the smaller negatively charged nucleophiles are more solvated by the usual polar solvents; that is, because the negative charge of Cl^- is more concentrated than the charge of I^-, the former is more tightly surrounded by a shell of solvent molecules which constitute a barrier between it and the substrate. This is most important for protic polar solvents, in which the solvent may hydrogen-bond to small nucleophiles. Evidence for this is that many nucleophilic substitutions with small negatively charged nucleophiles are much more rapid in aprotic polar solvents than in protic ones[96] and that, in dimethylformamide, an aprotic solvent, the order of nucleophilicity was $Cl^- > Br^- > I^-$.[97] Another experiment which supports this idea was the use of $Bu_4N^+X^-$ and LiX as nucleophiles in acetone, where X^- was a halide ion. The halide ion in the former salt is much less associated than in LiX. The relative rates with LiX were Cl^-, 1; Br^-, 5.7; I^-, 6.2, which is in the normal order, while with $Bu_4N^+X^-$, where X^- is much freer, the relative rates were Cl^-, 68; Br^-, 18; I^-, 3.7.[98]

However, solvation is not the entire answer, since even for *uncharged* nucleophiles, nucleophilicity increases going down a column in the periodic table. These nucleophiles are not so greatly solvated, and changes in solvent do not greatly affect their nucleophilicity.[99] Even with the charged nucleophiles ArO^- and ArS^-, changes in solvent did not affect the order. The other explanation is based on the greater polarizability of large nucleophiles.[94]

4. The freer the nucleophile, the greater the rate. We have already seen one instance of this.[98] Another is that the rate of attack by $(EtOOC)_2CBu^-\ \ Na^+$ in benzene was increased by the addition of substances (for example, Me_3PO, dimethylformamide) which specifically solvated the

---

[96] Parker, *J. Chem. Soc.* **1961**, 1328, has a list of about twenty such reactions.

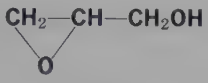
[97] Weaver and Hutchison, *J. Am. Chem. Soc.* **86**, 261 (1964).

[98] Winstein, Savedoff, Smith, Stevens, and Gall, *Tetrahedron Letters* **1960**, No. 9, 24.

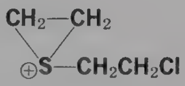
[99] Parker, *J. Chem. Soc.* **1961**, 4398.

Na^+ and thus left the anion freer.[100] In a nonpolar solvent such as benzene, salts such as $(EtOOC)_2CBu^-$ Na^+ usually exist as ion-pair aggregations of molecular weights of at least 10,000. Similarly, it was shown that the half-life of the reaction between $C_6H_5COCHEt^-$ and ethyl bromide depended on the positive ion: K^+, 4.5×10^{-3}; Na^+, 3.9×10^{-5}; Li^+, 3.1×10^{-7}.[101] Presumably, the potassium ion leaves the negative ion most free to attack most rapidly.

However, these four rules do not always hold. Steric influences play a part, and there are some anomalies which are not easily explained. For example, toward the substrate **25**, I^- is 10 times as reactive as OH^-, while toward **26**, OH^- is 12 times as reactive as I^- (both reactions involve ring opening) in the same solvent.[102]



25



26

The following overall nucleophilicity order, for S_N2 mechanisms, was given by Edwards and Pearson:[94] $RS^- > ArS^- > I^- > CN^- > OH^- > N_3^- > Br^- > ArO^- > Cl^- >$ pyridine $> AcO^- > H_2O$. A quantitative relationship has been worked out by Swain and Scott[103] similar to the linear free-energy equations considered in Chapter 9:

$$\log \frac{k}{k_0} = sn$$

where n is the nucleophilicity of a given group, s the sensitivity of a substrate to nucleophilic attack, and k_0 is the rate for H_2O, which is taken as the standard and for which n is assigned a value of zero. s is defined as 1.0 for methyl bromide. Table 5 contains values of n for some common nucleophiles. The order is similar to that of Edwards and Pearson.

For substitution at a carbonyl carbon, the nucleophilicity order is not the same but follows the basicity order more closely. This is presumably because the carbonyl carbon, with its partial positive charge, resembles a proton more than does the carbon at a saturated center. The following nucleophilicity order for these substrates has been determined:[104] $Me_2C{=}NO^- > EtO^- > MeO^- > OH^- > OAr^- > N_3^- > F^- > H_2O > Br^- \sim I^-$.

If, adjacent to the attacking atom on the nucleophile there is an atom containing one or more unshared pairs, the nucleophilicity is enhanced. Examples

---

[100] Zaugg, Horrom, and Borgwardt, *J. Am. Chem. Soc.* **82,** 2895 (1960); Zaugg, *J. Am. Chem. Soc.* **82,** 2903 (1960).

[101] Zook and Gumby, *J. Am. Chem. Soc.* **82,** 1386 (1960).

[102] Ogston, Holiday, Philpot, and Stocken, *Trans. Faraday Soc.* **44,** 45 (1948).

[103] Swain and Scott, *J. Am. Chem. Soc.* **75,** 141 (1953).

[104] Hudson and Green, *J. Chem. Soc.* **1962,** 1055; Bender and Glasson, *J. Am. Chem. Soc.* **81,** 1590 (1959).

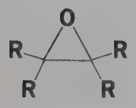
TABLE 5. Nucleophilicities of some common reagents[105]

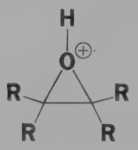
Nucleophile	*n*	*Nucleophile*	*n*
SH^-	5.1	Br^-	3.5
CN^-	5.1	PhO^-	3.5
I^-	5.0	AcO^-	2.7
$PhNH_2$	4.5	Cl^-	2.7
OH^-	4.2	NO_3^-	1.0
N_3^-	4.0	H_2O	0.0
Pyridine	3.6		

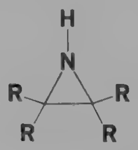
of such nucleophiles are HO_2^-, $Me_2C{=}NO^-$, NH_2NH_2, etc. This is called the *alpha effect*,[94] and the reasons for it are not completely understood.

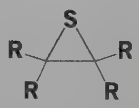
The Effect of the Leaving Group. The leaving group comes off more easily the more stable it is as a free entity. This is usually inverse to its basicity, and the best leaving groups are the weakest bases. Thus iodide is the best leaving group among the halides, and fluoride the poorest. Since XH is always a weaker base than X^-, nucleophilic substitution is always easier at a substrate RXH^+ than at RX. An example of this effect is that OH and OR are not leaving groups from ordinary alcohols and ethers, but can come off when the groups are protonated, that is, converted to ROH_2^+ or $RORH^+$. Reactions in which the leaving group does not come off until it has been protonated are called S_N1cA or S_N2cA, depending on whether the reaction, after protonation, is an S_N1 or S_N2 process (sometimes these designations are shortened to A1 and A2). The cA stands for conjugate acid, since the substitution takes place on the conjugate acid of the substrate.

Another circumstance that increases leaving-group power is ring strain. Ordinary ethers do not cleave at all, and protonated ethers only under strenuous conditions, but epoxides are cleaved quite easily, and protonated









epoxides even more easily. Aziridines and episulfides, three-membered rings containing, respectively, nitrogen and sulfur, are also easily cleaved.

Probably the best leaving group is N_2 from the species RN_2^+, which can be generated in several ways, of which the two most important are the treatment of primary amines with nitrous acid (see p. 484 for this reaction)

$$RNH_2 + HONO \longrightarrow RN_2^+$$

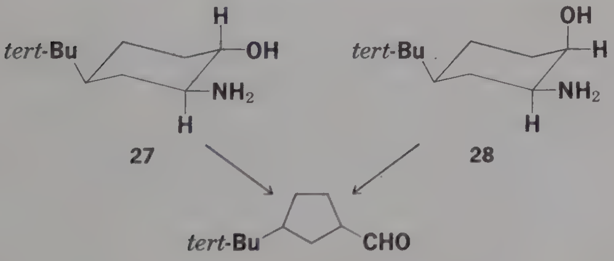
---

[105] From Wells, *Chem. Rev.* **63**, 171–219 (1963), p. 212.

and the protonation of diazo compounds

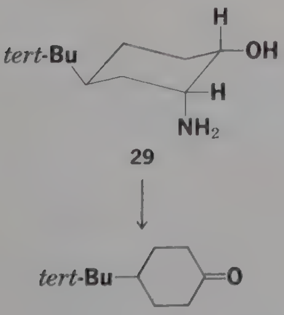
$$R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} + H^+ \longrightarrow R_2CHN_2^+$$

No matter how produced, RN_2^+ are too unstable to be isolable,[106] reacting presumably by the S_N1 or S_N2 mechanism. Actually the exact mechanisms are in doubt because the rate laws, stereochemistry, and products have proved difficult to interpret.[107] If there are free carbonium ions, they should give the same ratio of substitution to elimination to rearrangements, etc., as carbonium ions generated in other S_N1 reactions, but they often do not. "Hot" carbonium ions (unsolvated and/or chemically activated) which can hold their configuration have been postulated.[108] These carbonium ions have very short lifetimes, even when compared to what are formally the same carbonium ions generated in other ways, and the products are determined, not by the same factors, but largely by the conformation of the original molecule. A series of experiments which demonstrated this was carried out by Chérest and coworkers.[109] They showed, by the use of conformationally rigid molecules, that deamination is highly stereoselective. The four isomeric 4-*tert*-butyl-2-aminocyclohexanols were treated with nitrous acid, and in each case only one product was obtained:

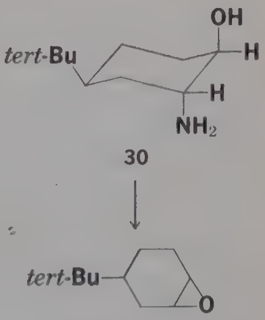


27

28



29



30

---

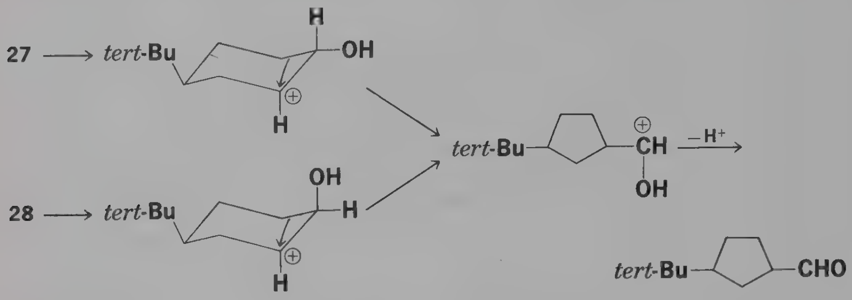
[106] *Aromatic* diazonium salts can, of course, be isolated (see Chapter 13), but only a few aliphatic diazonium salts have been prepared. See Reimlinger, *Angew. Chem. Intern. Ed. Engl.* **2**, 482 (1963); Bott, *Angew. Chem. Intern. Ed. Engl.* **3**, 804 (1964); *Tetrahedron* **22**, 1251 (1966).

[107] Streitwieser and Coverdale, *J. Am. Chem. Soc.* **81**, 4275 (1959).

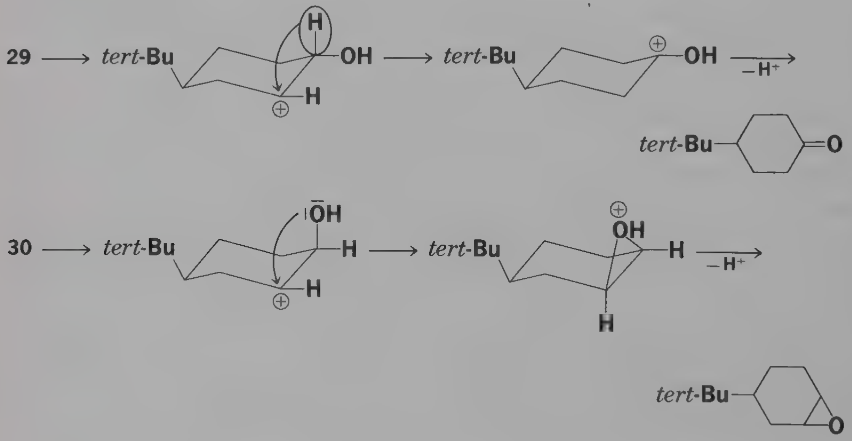
[108] For example, see Collins and Benjamin, *J. Am. Chem. Soc.* **85**, 2519 (1963).

[109] Chérest, Felkin, Sicher, Šipoš, and Tichý, *J. Chem. Soc.* **1965**, 2513.

For **27** and **28** the 2-hydrogen of the carbonium ion remains axial, and the different positions of the hydroxyl group and of the 1-hydrogen do not affect the product:



For **29** and **30**, the 2-hydrogen remains equatorial and prevents ring contraction. In each of these cases, the axial group at the 1-position forms a bond with the carbonium-ion carbon:



It is obvious that the carbonium ion does not reach its maximum stability before the product-determining step occurs.

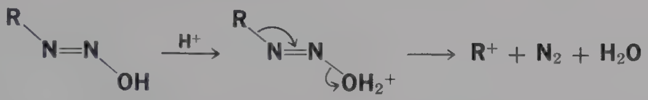
Diazonium ions generated from ordinary aliphatic primary amines are usually useless for preparative purposes, since they lead to a mixture of products, giving not only substitution by any nucleophile present, but also elimination and rearrangements if the substrate permits. For example, diazotization of *n*-butylamine gave 25% 1-butanol, 5.2% 1-chlorobutane, 13.2% 2-butanol, 36.5% butenes (consisting of 71% 1-butene, 20% *trans*-2-butene, and 9% *cis*-2-butene), and traces of butyl nitrites.[110]

It has been suggested[111] that the reaction between aliphatic amines and nitrous acid may lead to carbonium ions *without* the intermediacy of diazonium ions. This could happen if the C—N bond of the diazohydroxide (see p. 485 for the mechanism of diazonium-ion formation) is cleaved at the same time as the N—O bond:

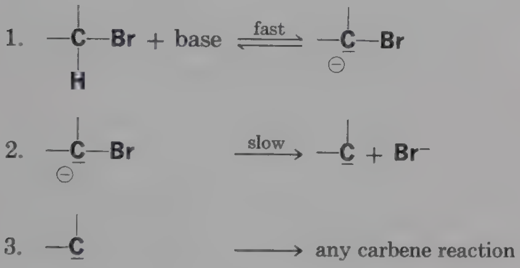
---

[110] Whitmore and Langlois, *J. Am. Chem. Soc.* **54**, 3441 (1932); Streitwieser and Schaeffer, *J. Am. Chem. Soc.* **79**, 2888 (1957).

[111] Ref. 109. Also see Cram and Sahyun, *J. Am. Chem. Soc.* **85**, 1257 (1963); and Maskill, Southam, and Whiting, *Chem. Commun.* **1965**, 496.



In the S_N1cA and S_N2cA mechanisms (p. 290) there is a preliminary step, the addition of a proton, before the normal S_N1 or S_N2 process occurs. There are also reactions in which the substrate *loses* a proton in a preliminary step. In these reactions there is a carbene intermediate:



$$1.\quad -\overset{|}{\underset{H}{C}}-Br + \text{base} \xrightleftharpoons{\text{fast}} -\overset{|}{\underset{\ominus}{\underline{C}}}-Br$$

$$2.\quad -\overset{|}{\underset{\ominus}{\underline{C}}}-Br \xrightarrow{\text{slow}} -\overset{|}{\underline{C}} + Br^-$$

$$3.\quad -\overset{|}{\underline{C}} \longrightarrow \text{any carbene reaction}$$

Once formed by this process, the carbene may give any of the normal carbene reactions (see p. 164). When the net result is substitution, this mechanism may be called the S_N1cB (for conjugate base) mechanism.[112] Although the slow step is an S_N1 step, the reaction is second order; first order in substrate and first order in base.

Table 6 lists some leaving groups in approximate order of ability to leave. The order of leaving-group ability is about the same for S_N1 and S_N2 reactions.

The Effect of the Reaction Medium. In general it may be said for S_N1 reactions that the more polar the solvent, the faster will be the reaction, since the intermediate ions or ion pairs will be better solvated by more polar solvents. Also there is a greater charge in the transition state than in the starting compound (Table 7). However, this is not true where the substrate has a positive charge:

$$RX^+ \longrightarrow R^+ + X$$

In such cases, the positive charge is more spread out in the transition state than in the starting ion, and a greater solvent polarity should hinder the reaction (Table 7). This is indeed the case.[113] Even for solvents with about the same polarity, there is a difference between protic and aprotic solvents. S_N1 reactions of un-ionized substrates are more rapid in protic solvents, which

---

[112] Pearson and Edgington, *J. Am. Chem. Soc.* **84,** 4607 (1962).

[113] Hyne, *Can. J. Chem.* **39,** 1207 (1961).

TABLE 6. Leaving groups listed in approximate order of decreasing ability to leave Groups which are common leaving groups at saturated and carbonyl carbons are indicated

	Common leaving groups	
Substrate **RX**	*At saturated carbon*	*At carbonyl carbon*
$RN_2{}^+$	×	
$ROR'_2{}^+$ (oxonium ion)		
ROTs, etc.[114]	×	
RI	×	
RBr	×	
$ROH_2{}^+$	× (conjugate acid of alcohol)	
RCl	×	× (acyl halides)
$RORH^+$	× (conjugate acid of ether)	
$RONO_2$, etc.[114]	×	
$RSR'_2{}^+$		
$RNR'_3{}^+$	×	
RF		
$ROCOR'$	×	× (anhydrides)
$RNH_3{}^+$		
ROAr		× (aryl esters)
ROH		× (carboxylic acids)
ROR		× (alkyl esters)
RH		
RNH_2		× (amides)
RAr		
RR		

TABLE 7. Transition states for S_N1 reactions of charged and uncharged substrates, and for S_N2 reactions of the four charge types[115]

Reactants and transition states			*Change in the transition state relative to starting materials*	*How an increase in solvent polarity affects the rate*
S_N2	Type I	$RX + Y^- \longrightarrow Y^{\delta-} \cdots\cdots R \cdots\cdots X^{\delta-}$	Dispersed	Small decrease
	Type II	$RX + Y \longrightarrow Y^{\delta+} \cdots\cdots R \cdots\cdots X^{\delta-}$	Increased	Large increase
	Type III	$RX^+ + Y^- \longrightarrow Y^{\delta-} \cdots\cdots R \cdots\cdots X^{\delta+}$	Decreased	Large decrease
	Type IV	$RX^+ + Y \longrightarrow Y^{\delta+} \cdots\cdots R \cdots\cdots X^{\delta+}$	Dispersed	Small decrease
S_N1		$RX \longrightarrow R^{\delta+} \cdots\cdots X^{\delta-}$	Increased	Large increase
		$RX^+ \longrightarrow R^{\delta+} \cdots\cdots X^{\delta+}$	Dispersed	Small decrease

---

[114] ROTs, etc., includes esters of sulfuric and sulfonic acids in general, for example, $ROSO_2OH$, $ROSO_2OR$, $ROSO_2R$, etc. $RONO_2$, etc., includes inorganic-ester leaving groups, such as $ROPO(OH)_2$, $ROB(OH)_2$, etc.

can stabilize the carbonium ion by hydrogen bonding. Examples of protic solvents are water, alcohols, and carboxylic acids, while some polar aprotic solvents are dimethylformamide, dimethyl sulfoxide, acetonitrile, acetone, and nitrobenzene.

For S_N2 reactions, the effect of the solvent depends on which of the four charge types the reaction belongs to (p. 251). In Types I and IV, an initial charge is dispersed in the transition state, so that the reaction is hindered by polar solvents. In Type III initial charges are *decreased* in the transition state, so that the reaction is even more hindered by polar solvents. Only Type II, where the reactants are uncharged, but the transition state has built up a charge, is aided by polar solvents. These effects are summarized in Table 7.[115] For S_N2 reactions also, the difference between protic and aprotic solvents must be considered.[116] For reactions of Types I and III the transition state is more solvated in polar aprotic solvents than in protic ones, while the original charged nucleophile was less solvated in aprotic solvents. So the change from say, methanol to dimethyl sulfoxide should greatly increase the rate. As an example, the relative rates at 25° for the reaction between methyl iodide and Cl^- were[96] in MeOH, 1; in $HCONH_2$ (still protic though a weaker acid), 12.5; in HCONHMe, 45.3; and in $HCONMe_2$, 1.2×10^6. The change in rate in going from a protic to an aprotic solvent is also related to the *size* of the attacking anion. Small ions are solvated best in protic solvents, since hydrogen bonding is most important for them, while large anions are solvated best in aprotic solvents, since polarizability is greatest with large ions. So the rates of attack by small anions will be most greatly increased by the change from a protic to an aprotic solvent. This may have preparative significance. Reference 116 has a list of several dozen reactions of charge types I and III in which yields are improved and reaction times cut in polar aprotic solvents. Reaction types II and IV are much less susceptible to the difference between protic and aprotic solvents.

Since for most reactions, S_N1 rates go up and S_N2 rates go down in solvents of increasing polarity, it is quite possible for the same reaction to go by the S_N1 mechanism in one solvent and the S_N2 in another.

Table 8 is a list of solvents in order of ionizing power; a solvent high on the list is a good solvent for S_N1 reactions.

We have seen how the polarity of the solvent influences the rates of S_N1 and S_N2 reactions. The ionic strength of the medium has similar effects. In general, the addition of an external salt affects the rates of S_N1 and S_N2 reactions in the same way as an increase in solvent polarity, although this is not quantitative: different salts have different effects.[117] However, there are exceptions: although the rates of S_N1 reactions are usually increased by the addition of salts (this is called the *salt effect*), addition of the leaving-group ion often decreases the rate (the common-ion effect, p. 257). Also, there is

---

[115] This analysis is due to Ingold; see Ingold, "Structure and Mechanism in Organic Chemistry," pp. 345–350, Cornell University Press, Ithaca, N.Y., 1953.

[116] For a review of the effect of protic and aprotic solvents, see Parker, *Quart. Rev.* (*London*) **16**, 163–187 (1962).

[117] Duynstee, Grunwald, and Kaplan, *J. Am. Chem. Soc.* **82**, 5654 (1960).

TABLE 8. Relative rates of ionization of *p*-methoxyneophyl toluenesulfonate in various solvents[118]

Solvent	*Relative rate*	*Solvent*	*Relative rate*
HCOOH	153	Ac_2O	0.020
H_2O	39	Pyridine	0.013
80% EtOH-H_2O	1.85	Acetone	0.0051
AcOH	1.00	EtOAc	6.7×10^{-4}
MeOH	0.947	Tetrahydrofuran	5.0×10^{-4}
EtOH	0.370	Et_2O	3×10^{-5}
Me_2SO	0.108	$CHCl_3$	Lower still
Octanoic acid	0.043	Benzene	
MeCN	0.036	Alkanes	
$HCONMe_2$	0.029		

the special salt effect of $LiClO_4$ or LiBr (p. 259), which led to the idea of ion pairs. In addition to these effects, S_N1 rates are also greatly accelerated when there are ions present which specifically help in pulling off the leaving group. Especially important are Ag^+, Hg^{++}, and Hg_2^{++}, but H^+ helps to pull off F (hydrogen bonding).[119]

The effect of solvent has been treated quantitatively (for S_N1 mechanisms, in which the solvent pulls off the leaving group) by a linear free-energy relationship[120]

$$\log \frac{k}{k_0} = mY$$

where m is characteristic of the substrate (defined as 1.00 for *tert*-BuCl) and is usually near unity; Y is characteristic of the solvent and measures its "ionizing power"; and k_0 is the rate in a standard solvent, 80% aqueous ethanol at 25°. This is known as the Grunwald-Winstein equation, and its utility is, at best, limited. Y values can of course be measured for solvent *mixtures* too, and this is one of the principal advantages of the treatment, since it is not easy otherwise to assign a polarity arbitrarily to a given mixture of solvents. The treatment is most satisfactory for different proportions of a given solvent pair. For wider comparisons the treatment is not so good quantitatively, although the Y values do give a reasonably good idea of solvolyzing power. Table 9 contains a list of some Y values.

Other attempts have been made at correlating solvent polarities. Kosower found that the position of the charge-transfer peak (see p. 66) in the ultra-

---

[118] Smith, Fainberg, and Winstein, *J. Am. Chem. Soc.* **83**, 618 (1961).

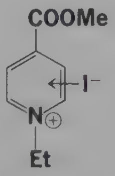
[119] Coverdale and Kohnstam, *J. Chem. Soc.* **1960**, 3906.

[120] Grunwald and Winstein, *J. Am. Chem. Soc.* **70**, 846 (1948). For reviews, see Reichardt, *Angew. Chem. Intern. Ed. Engl.* **4**, 29–40 (1965); and Ref. 105, pp. 202–215.

TABLE 9. *Y* and *Z* values for some solvents[121]

Solvent	*Y*	*Z*
H_2O	3.5	94.6
HCOOH	2.1	
H_2O-EtOH (1:1)	1.7	90
$HCONH_2$	0.6	83.3
80% EtOH	0.0	84.8
MeOH	−1.1	83.6
AcOH	−1.6	79.2
EtOH	−2.0	79.6
90% Dioxane	−2.0	76.7
iso-PrOH	−2.7	76.3
95% Acetone	−2.8	72.9
tert-BuOH	−3.3	71.3
MeCN		71.3
Me_2SO		71.1
$HCONMe_2$		68.5
Acetone		65.7
Pyridine		64.0

violet spectrum of the complex between iodide ion and 1-methyl- or 1-ethyl-4-carbomethoxypyridinium ion



was dependent on the polarity of the solvent.[122] From these peaks, which are very easy to measure, Kosower calculated transition energies, which he called *Z* values. *Z* values are thus measures of solvent polarity analogous to *Y* values. Table 9 shows that *Z* values are generally in the same order as *Y* values.

The effect of the solvent on the nucleophile has already been discussed (p. 288).

It may be recalled that Swain regarded all nucleophilic substitutions at a saturated carbon as proceeding by a mechanism in which the solvent pulls off the leaving group and the nucleophile pushes it off (p. 261). If the Grunwald-Winstein equation, which applies only to the solvolysis of the leaving group, is combined with the nucleophilicity relationship (p. 289), which only applies to pushing by the nucleophile, the following equation is obtained:

---

[121] *Y* values are from Fainberg and Winstein, *J. Am. Chem. Soc.* **78,** 2770 (1956). *Z* values are from Ref. 122.

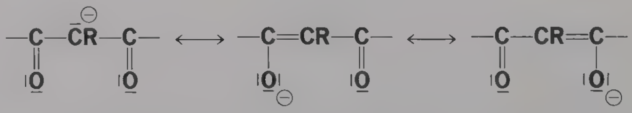
[122] Kosower, *J. Am. Chem. Soc.* **80,** 3253, 3261, 3267 (1958); Kosower and Wu, *J. Am. Chem. Soc.* **83,** 3142 (1961); Kosower, Wu, and Sorensen, *J. Am. Chem. Soc.* **83,** 3147 (1961).

$$\log \frac{k}{k_0} = sn + s'e$$

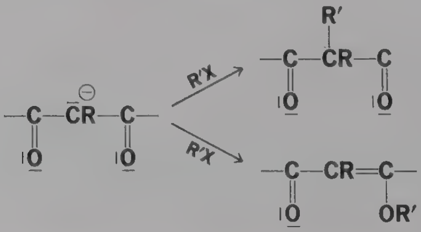
where s and n are as defined on page 289, s' is analogous to m, and e is analogous to Y.[103] In solvolysis reactions, the solvent may be both pushing and pulling, so that n and e are different functions of the same compound. This equation has not proved very satisfactory, and numerous attempts have been made to improve it.

Ambident Nucleophiles. Some nucleophiles have a pair of electrons on each of two or more atoms, or resonance forms may be drawn in which two or more atoms bear an unshared pair. In these cases the nucleophile may attack in two or more different ways to give different products. Such reagents are called *ambident nucleophiles.* In most cases a nucleophile with two potentially attacking atoms can attack with either of them, depending on conditions, and mixtures are often obtained, though this is not always the case. For example, the nucleophile NCO^- gives only isocyanates RNCO and not the isomeric cyanates ROCN. Some important ambident nucleophiles are:

1. *Ions of the type* $—\text{CO}—\overset{\ominus}{\bar{\text{C}}}\text{R}—\text{CO}—$. These ions, which are derived by removal of a proton from malonic esters, β-keto esters, β-diketones, etc., are resonance hybrids:

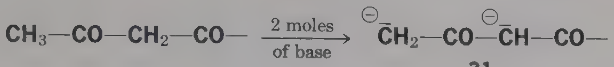


They can thus attack a saturated carbon with their carbon atoms (C-alkylation) or with their oxygen atoms (O-alkylation):



With unsymmetrical ions, three products are possible, since either oxygen may attack. With a carbonyl substrate the ion may analogously undergo C-acylation or O-acylation.

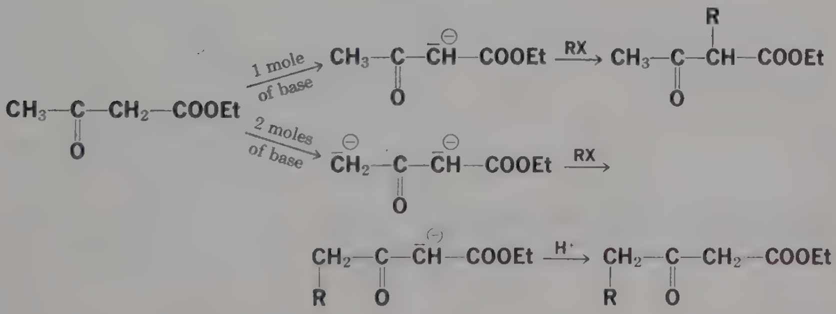
2. *Compounds of the type* $CH_3CO—CH_2—CO—$. These can give up two protons, if treated with two moles of a strong enough base, to give dicarbanions:



$$CH_3—CO—CH_2—CO— \xrightarrow[\text{of base}]{\text{2 moles}} \overset{\ominus}{\bar{C}}H_2—CO—\overset{\ominus}{\bar{C}}H—CO—$$

31

Such ions are ambident nucleophiles, since they have two possible attacking carbon atoms, aside from the possibility of attack by oxygen. In such cases, the attack is always by the more basic carbon. Since the hydrogen of a carbon bonded to two carbonyl groups is more acidic than that of a carbon bonded to just one (see Chapter 8), the CH group of **31** is less basic than the CH_2 group, so that the latter attacks the substrate. This gives rise to a useful general principle: whenever it is desired to remove a proton at a given position for use as a nucleophile, but there is a stronger acidic group in the molecule, it may be possible to take off both protons; if it is, then attack is always by the desired position, since it is the ion of the weaker acid. On the other hand, if it is desired to attack with the more acidic position, all that is necessary is to remove just one proton.[123] For example, ethyl acetoacetate may be alkylated at will, either at the methyl or at the methylene group (reaction **0-86**):



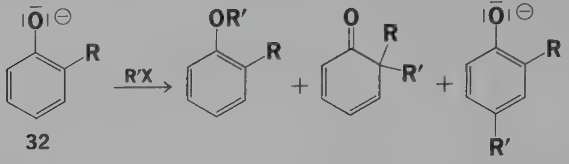
3. *The* CN^- *ion.* This nucleophile may give nitriles RCN (reaction **0-88**) or isonitriles RN≡C.

4. *The nitrite ion.* This ion may give nitrite esters R—O—N=O (reaction **0-32**) or nitro compounds RNO_2 (reaction **0-59**), which are not esters.

---

[123] This principle has been applied many times by Hauser and coworkers; see, for example, Hauser and Harris, *J. Am. Chem. Soc.* **80,** 6360 (1958); Hamrick and Hauser, *J. Am. Chem. Soc.* **82,** 1957 (1960); O'Sullivan, Tavares, and Hauser, *J. Am. Chem. Soc.* **83,** 3453 (1961); Bryant and Hauser, *J. Am. Chem. Soc.* **83,** 3468 (1961); Harris, Boatman, and Hauser, *J. Am. Chem. Soc.* **85,** 3273 (1963); Work, Bryant, and Hauser, *J. Am. Chem. Soc.* **86,** 872 (1964), *J. Org. Chem.* **29,** 722 (1964); Boatman, Harris, and Hauser, *J. Am. Chem. Soc.* **87,** 82 (1965); Meyer and Hauser, *J. Org. Chem.* **25,** 158 (1960), **26,** 3696 (1961); Kofron, Dunnavant, and Hauser, *J. Org. Chem.* **27,** 2737 (1962); Hampton, Harris, and Hauser, *J. Org. Chem.* **28,** 1946 (1963), **31,** 663, 1035 (1966); Miles, Harris, and Hauser, *J. Org. Chem.* **30,** 1007 (1965); and Hampton, Light, and Hauser, *J. Org. Chem.* **30,** 1413 (1965).

5. Phenolate ions (**32**) may undergo C-alkylation or O-alkylation:



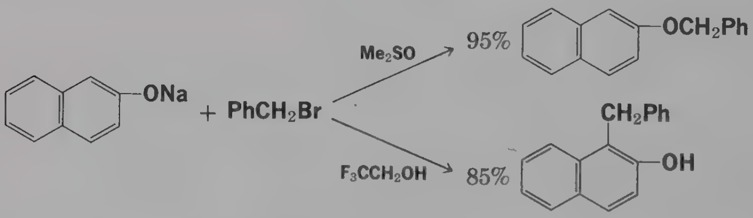
32

There are many other ambident nucleophiles. An interesting case is that of β-amino-α,β-unsaturated ketones, which may be alkylated on a carbon, oxygen, or nitrogen atom.[124]

It would be useful to have general rules as to which end of an ambident nucleophile will attack a given substrate under a given set of conditions. Unfortunately, such rules as have been proposed usually turn out to have a great many exceptions.[125] However, the following points can be made:

1. With the nucleophile CN^-, the use of Ag^+ promotes attack at the more electronegative atom, in this case nitrogen, so that higher yields of isonitriles RNC are obtained. On the other hand, with NO_2^- and primary halides, the use of Ag^+ results in higher yields of RNO_2, so that in this case attack by the less electronegative atom is favored.[126]

2. In protic solvents the more electronegative atom will be solvated; hence attack is often by the less electronegative atom. Thus the attack by sodium β-naphthoxide on benzyl bromide resulted in 95% O-alkylation in dimethyl sulfoxide and 85% C-alkylation in 2,2,2-trifluoroethanol.[127]



3. When sulfur competes with a first-row atom, the sulfur usually attacks, though exceptions are known.[128]

4. In some cases steric influences control. Thus the 2,6-di-*tert*-butylphenoxide ion gave 88% O-alkylation and 6% C-alkylation with methyl iodide; 11%

---

[124] Leonard and Adamcik, *J. Am. Chem. Soc.* **81,** 595 (1959).

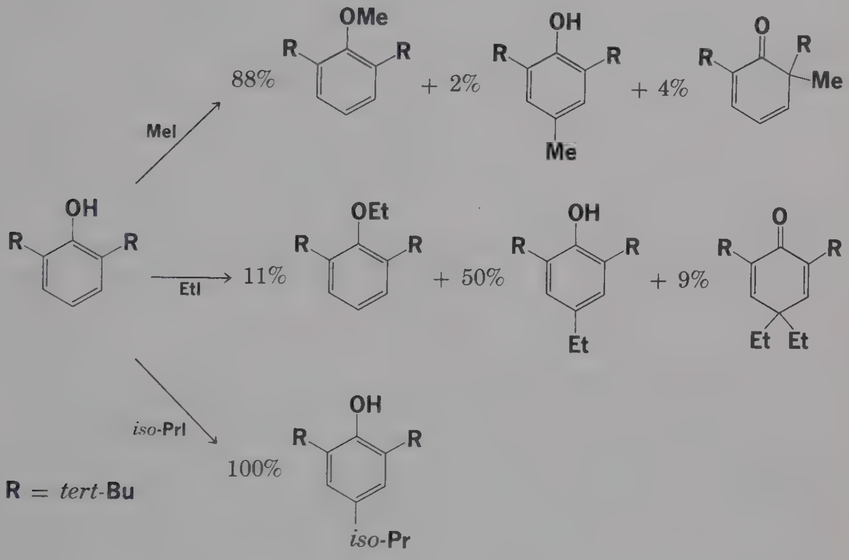
[125] For discussions of this, see Curtin and Fraser, *J. Am. Chem. Soc.* **80,** 6016 (1958); Curtin, Crawford, and Wilhelm, *J. Am. Chem. Soc.* **80,** 1391 (1958); Kornblum, Smiley, Blackwood, and Iffland, *J. Am. Chem. Soc.* **77,** 6269 (1955); Curtin and Dybvig, *J. Am. Chem. Soc.* **84,** 225 (1962). For a review, see Gompper, *Angew. Chem. Intern. Ed. Engl.* **3,** 560–570 (1964).

[126] Kornblum, *Org. Reactions* **12,** 101–156 (1962).

[127] Kornblum, Berrigan, and le Noble, *J. Am. Chem. Soc.* **85,** 1141 (1963); Kornblum, Seltzer, and Haberfield, *J. Am. Chem. Soc.* **85,** 1148 (1963). See also le Noble and Puerta, *Tetrahedron Letters* **1966,** 1087.

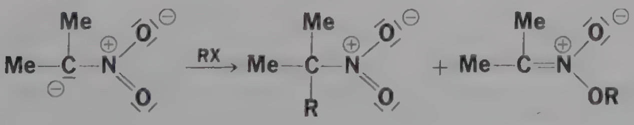
[128] Miller and O'Leary, *J. Org. Chem.* **27,** 3382 (1962).

O- and 59% C-alkylation with ethyl iodide; and 100% C-alkylation with isopropyl iodide:



although the unsubstituted phenoxide ion gave only O-alkylation with all three alkyl halides.[129]

5. In at least one case the *leaving group* made a substantial difference. In the alkylation of $Me_2\overset{\ominus}{C}NO_2$ with *p*-$O_2NC_6H_4CH_2X$, for X = Cl there resulted 95% C-alkylation and 1% O-alkylation, but for X = I there was 9% C-alkylation and 81% O-alkylation, with other leaving groups giving in-between values.[130]



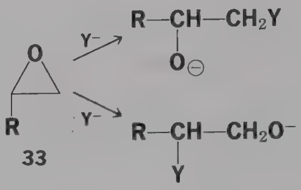
X = Cl	95%	1%
X = OTs	40%	32%
X = Br	17%	65%
X = I	9%	81%

---

[129] Kornblum and Seltzer, *J. Am. Chem. Soc.* **83,** 3668 (1961).

[130] Kornblum, Pink, and Yorka, *J. Am. Chem. Soc.* **83,** 2779 (1961); Kornblum and Pink, *Tetrahedron* **19,** Suppl. 1, 17 (1963).

Ambident Substrates. Some substrates (for example, 1,3-dichlorobutane) may be attacked at two or more positions. We may call these *ambident substrates.* In the example given, there happen to be two leaving groups in the molecule, but there are two kinds of substrates which are inherently ambident (unless symmetrical). One of these, the allylic type, has already been discussed (p. 270). The other is the epoxy (or the similar aziridine or episulfide) substrate.[131]



33

Substitution of the free epoxide, which generally occurs under basic or neutral conditions, usually involves an S_N2 mechanism. Since primary substrates undergo S_N2 attack more readily than secondary, compounds of the type **33** will be attacked in neutral or basic solution at the less highly substituted carbon, and stereospecifically, with inversion at that carbon. Under acidic conditions, it is the protonated epoxide which undergoes the reaction. Under these conditions the mechanism may be either S_N1 or S_N2. In S_N1 mechanisms, which favor tertiary carbons, we might expect that attack would be at the more highly substituted carbon, and this is indeed the case. However, even when protonated epoxides react by the S_N2 mechanism, attack is usually at the more highly substituted position.[132] Thus, it is often possible to change the direction of ring opening by changing the conditions from basic to acidic or vice versa.

REACTIONS

The reactions in this chapter are classified according to the attacking atom of the nucleophile in the order O, S, N, halogen, H, C. For a given nucleophile, reactions are classified by the substrate and leaving group, with alkyl substrates usually considered before acyl ones. Nucleophilic substitutions at a sulfur atom are treated at the end.

Not all the reactions in this chapter are actually nucleophilic substitutions. In some cases the mechanisms are not known with enough certainty even to decide whether a nucleophile, an electrophile, or a free radical is attacking.

---

[131] For reviews of substitution at this type of substrate, see Parker and Isaacs, *Chem. Rev.* **59**, 737–799 (1959), and Winstein and Henderson, in Elderfield, "Heterocyclic Compounds," vol. 1, pp. 22–39, John Wiley & Sons, Inc., New York, 1950.

[132] Addy and Parker, *J. Chem. Soc.* **1963**, 915.

In other cases (such as **0-73**) conversion of one compound to another may occur by two or even all three of these possibilities, depending on the reagent and on the reaction conditions. However, one or more of the nucleophilic mechanisms previously discussed do hold for the overwhelming majority of the reactions in this chapter.

Oxygen Nucleophiles

A. Attack by OH at an alkyl carbon

0-1 Hydrolysis of alkyl halides

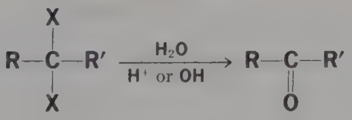
$$\mathrm{RX} + \mathrm{H_2O} \longrightarrow \mathrm{ROH_2}^+ \xrightarrow{-\mathrm{H}^+} \mathrm{ROH} + \mathrm{H}^+$$

$$\mathrm{RX} + \mathrm{OH}^- \longrightarrow \mathrm{ROH}$$

Alkyl halides may be hydrolyzed to alcohols. Hydroxide ion is usually required, except that especially active substrates, such as allylic or benzylic types, may be hydrolyzed by water. In contrast to most nucleophilic substitutions at saturated carbons, this reaction can be performed on tertiary substrates without significant interference from elimination side reactions. The reaction is not frequently used for synthetic purposes, because alkyl halides are usually obtained from alcohols.

OS **II,** 408; **III,** 434; **IV,** 128.

0-2 Hydrolysis of *gem*-dihalides



$$\mathrm{R{-}CX_2{-}R'} \xrightarrow[\mathrm{H^+\ or\ OH}]{\mathrm{H_2O}} \mathrm{R{-}C({=}O){-}R'}$$

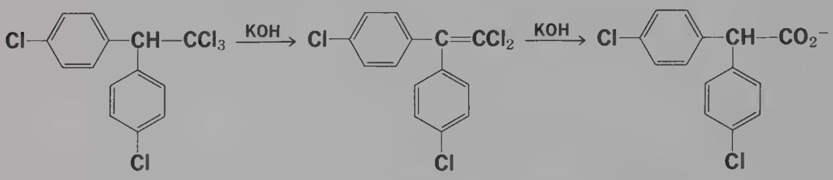
gem-Dihalides may be hydrolyzed, with either acid or basic catalysis, to give aldehydes or ketones. Formally, the reaction may be regarded as first giving R—C(OH)XR′, which is unstable and loses HX to give the carbonyl compound. This is a very good reaction for the preparation of aromatic aldehydes, but for ketones and aliphatic aldehydes the starting dihalides are not easy to prepare. For aldehydes, strong bases may not be used, because the product undergoes the aldol condensation (**6-39,** p. 692) or the Cannizzaro reaction (**9-62,** p. 908).

OS **I,** 95; **II,** 89, 133, 244, 549; **III,** 538, 788; **IV,** 110, 423, 807. Also see OS **III,** 737.

0-3 Hydrolysis of 1,1,1-trihalides

$$RCX_3 + H_2O \longrightarrow RCOOH$$

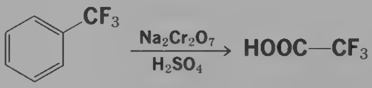
This reaction is similar to the previous one. Formally, $RC(OH)X_2$ may be regarded as an intermediate, which loses HX to give RCOX, which is easily hydrolyzed to the acid under the reaction conditions. However, in at least one case, that of treatment of DDT with KOH, elimination takes place first, since **34** can be isolated (OS **III**, 270):



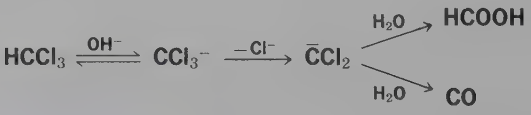
DDT **34**

The utility of the method is limited by lack of availability of trihalides.

Trifluorides do not undergo this reaction. As an example of the remarkable stability of the C—F bond to nucleophilic substitution, α,α,α-trifluorotoluene, treated for two weeks with sodium dichromate and sulfuric acid, gave trifluoroacetic acid.



Chloroform is more rapidly hydrolyzed with base than is dichloromethane or carbon tetrachloride and gives not only formic acid but also carbon monoxide. Hine[133] has shown that the mechanism of chloroform hydrolysis is quite different from that of dichloromethane or carbon tetrachloride, though superficially the three reactions appear similar. The first step is the loss of a proton to give CCl_3^-, which then loses Cl^- to give CCl_2, which is hydrolyzed to formic acid or carbon monoxide:



This is an example of an S_N1cB mechanism (p. 293). The other two compounds react by the normal mechanisms. Carbon tetrachloride cannot give up a proton, and dichloromethane is not acidic enough.

OS **III**, 270. Also see OS **I**, 327.

---

[133] Hine, *J. Am. Chem. Soc.* **72**, 2438 (1950). Also see le Noble, *J. Am. Chem. Soc.* **87**, 2434 (1965).

0-4 Hydrolysis of alkyl esters of inorganic acids

$$\left.\begin{array}{l} R{-}OSO_2OH \\ R{-}OSO_2OR' \\ R{-}OSO_2R' \\ R{-}OSOOH \\ R{-}OSOOR' \\ R{-}OSOR' \\ R{-}ONO_2 \\ R{-}ONO \\ R{-}OPO(OH)_2 \\ R{-}OPO(OR')_2 \\ R{-}OB(OH)_2 \\ \text{and others} \end{array}\right\} \xrightarrow{H_2O} R{-}OH$$

Esters of inorganic acids, including those given above and others, can be hydrolyzed to alcohols. The reactions are most successful where the ester is that of a strong acid, but it can be done for esters of weaker acids by the use of hydroxide ion (a more powerful nucleophile) or acid conditions (which make the leaving group come off more easily).

These reactions are all considered at one place because they are formally similar, but, although some of them involve R—O cleavage and are thus nucleophilic substitutions at a saturated carbon, others involve cleavage of the bond between the inorganic atom and oxygen and are thus nucleophilic substitutions at a sulfur, nitrogen, etc. It is even possible for the same ester to be cleaved at either position depending on the conditions. Thus benzhydryl *p*-toluenesulfinate ($Ph_2CHOSOC_6H_4CH_3$) was found to undergo C—O cleavage in $HClO_4$ solutions and S—O cleavage in alkaline media.[134] In general, the weaker the corresponding acid, the less likely is C—O cleavage. Thus, sulfonic acid esters, $ROSO_2R'$, generally give C—O cleavage,[135] while nitrous acid esters, RONO, usually give N—O cleavage.[136] Two important types of sulfonic acid esters are *tosylates* (ROTs; *p*-$ROSO_2C_6H_4CH_3$) and *brosylates* (ROBs; *p*-$ROSO_2C_6H_4Br$). For hydrolysis of sulfonic acid esters, also see reaction **0-99**.

0-5 Diazotization of primary aliphatic amines

$$RNH_2 + HONO \longrightarrow RN_2^+ \xrightarrow{H_2O} N_2 + ROH + \text{other products}$$

The diazotization of primary amines is not usually a good method for the preparation of alcohols, since it leads to a mixture of products (see p. 292). The reaction can be used, however, to measure the amount of NH_2 present in a sample, since nitrogen is evolved quantitatively.

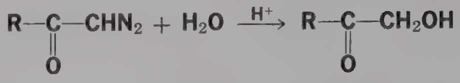
---

[134] Bunton and Hendy, *J. Chem. Soc.* **1963,** 627.

[135] Barnard and Robertson, *Can. J. Chem.* **39,** 881 (1961).

[136] Allen, *J. Chem. Soc.* **1954,** 1968.

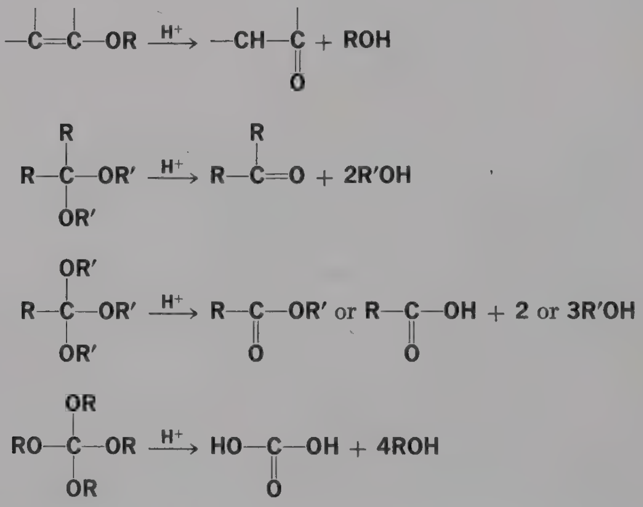
0-6 Hydrolysis of diazo ketones



$$R-\underset{\underset{\displaystyle O}{\|}}{C}-CHN_2 + H_2O \xrightarrow{H^+} R-\underset{\underset{\displaystyle O}{\|}}{C}-CH_2OH$$

Diazo ketones are relatively easy to prepare (see reaction **0-97**). When treated with acid, they add a proton to give diazonium salts, which are hydrolyzed to the alcohols by the S_N1 mechanism.[137] Relatively good yields of α-hydroxy ketones may be prepared in this way, since the diazonium ion is somewhat stabilized by the carbonyl group.

0-7 Hydrolysis of vinyl ethers, acetals, and ortho esters



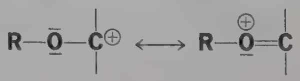
$$-\overset{|}{C}=\overset{|}{C}-OR \xrightarrow{H^+} -CH-\underset{\underset{\displaystyle O}{\|}}{\overset{|}{C}} + ROH$$

$$R-\underset{\underset{\displaystyle OR'}{|}}{\overset{\overset{\displaystyle R}{|}}{C}}-OR' \xrightarrow{H^+} R-\overset{\overset{\displaystyle R}{|}}{C}=O + 2R'OH$$

$$R-\underset{\underset{\displaystyle OR'}{|}}{\overset{\overset{\displaystyle OR'}{|}}{C}}-OR' \xrightarrow{H^+} R-\underset{\underset{\displaystyle O}{\|}}{C}-OR' \text{ or } R-\underset{\underset{\displaystyle O}{\|}}{C}-OH + 2 \text{ or } 3R'OH$$

$$RO-\underset{\underset{\displaystyle OR}{|}}{\overset{\overset{\displaystyle OR}{|}}{C}}-OR \xrightarrow{H^+} HO-\underset{\underset{\displaystyle O}{\|}}{C}-OH + 4ROH$$

The alkoxyl group OR is not a leaving group, and so these compounds must be converted to the conjugate acids before they can be hydrolyzed. Although 100% sulfuric acid and other concentrated strong acids readily cleave simple ethers,[138] the only acids used preparatively for this purpose are HBr and HI (reaction **0-65**). However, acetals, ketals, and ortho esters are easily cleaved by dilute acids. These compounds are hydrolyzed with greater facility because carbonium ions of the type **35** are greatly stabilized by resonance. The reactions therefore proceed by the S_N1 mechanism. Acetals, ketals, and ortho esters are extremely resistant to hydrolysis by bases.



$$R-\underline{\overline{O}}-\underset{|}{\overset{|}{C}}{}^{\oplus} \longleftrightarrow R-\overset{\oplus}{\underline{O}}=\underset{|}{\overset{|}{C}}$$

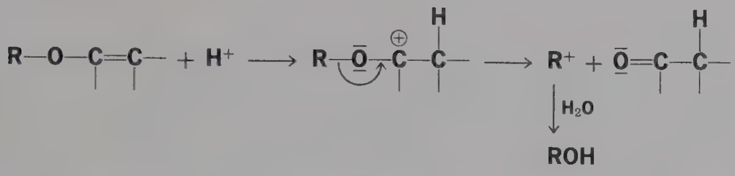
35

---

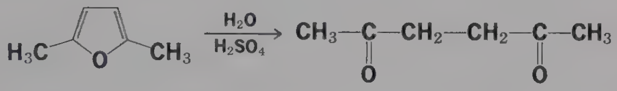
[137] Dahn and Gold, *Helv. Chim. Acta* **46,** 983 (1963); Dahn, Donzel, Merbach, and Gold, *Helv. Chim. Acta* **46,** 994 (1963).

[138] Jaques and Leisten, *J. Chem. Soc.* **1964,** 2683.

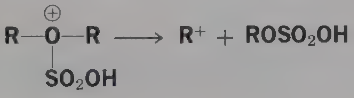
Vinyl ethers are readily hydrolyzed by acids because the leaving group is an aldehyde or ketone. The first step is protonation not of the oxygen, but of the β-carbon:[139]



Furans represent a special case of vinyl ethers which are cleaved by acid to give 1,4-diones. Thus



Mixed aryl alkyl ethers have been cleaved in 99.6% H_2SO_4, by a simple S_N1 mechanism. Dialkyl ethers have also been cleaved in this medium, but in this case the ether first reacted with SO_3 to give **36,** so that the leaving group is $ROSO_2OH$.[140] *tert*-Butyl ethers are readily cleaved with perfluoroacetic acid.[141] This is not a nucleophilic substitution, but an elimination, the *tert*-butyl group being converted to isobutylene (also see reaction **7-2,** p. 755):



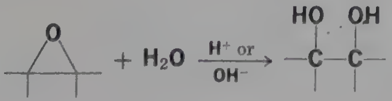
$$R-\overset{\oplus}{\underset{SO_2OH}{O}}-R \longrightarrow R^+ + ROSO_2OH$$

36

$$ROC(CH_3)_3 \xrightarrow{F_3COOH} ROH + (CH_3)_2C{=}CH_2$$

OS **I,** 67, 205; **II,** 302, 305, 323; **III,** 37, 127, 465, 470, 536, 541, 564, 641, 701, 731, 800; **IV,** 302, 499, 660, 816, 903; **40,** 14; **42,** 34; **43,** 68; **44,** 94. Also see OS **42,** 87.

0-8 Hydrolysis of epoxides



---

[139] Jones and Wood, *J. Chem. Soc.* **1964,** 5400.

[140] Jaques and Leisten, *J. Chem. Soc.* **1961,** 4963.

[141] Beyerman and Bontekoe, *Rec. trav. chim.* **81,** 691 (1962); Beyerman and Heiszwolf, *Rec. trav. chim.* **84,** 203 (1965); Callahan, Anderson, Paul, and Zimmerman, *J. Am. Chem. Soc.* **85,** 201 (1963).

The hydrolysis of epoxides is a convenient method for the preparation of *vic*-glycols. The reaction is catalyzed by acids or bases (see discussion of mechanism on p. 302). Dimethyl sulfoxide is a superior solvent for the alkaline hydrolysis of epoxides.[142]

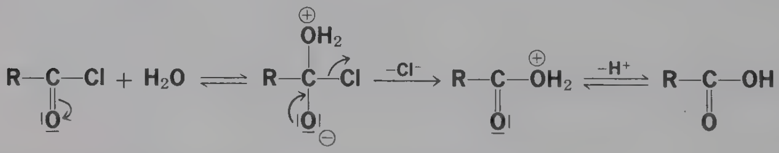
OS **42,** 50.

B. Attack by OH at an acyl carbon

0-9 Hydrolysis of acyl halides

$$RCOCl + H_2O \longrightarrow RCOOH$$

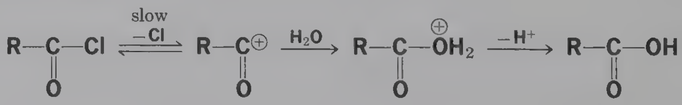
The hydrolysis of acyl halides is easily carried out.[143] Water is usually a strong enough nucleophile, but in difficult cases hydroxide ion may be required. The reaction is seldom synthetically useful, because acyl chlorides are normally prepared from acids. If a carboxylic acid is used as the nucleophile, an exchange reaction may take place (see reaction **0-70**). The mechanism of hydrolysis may be either S_N1 or tetrahedral, the former occurring in highly polar solvents and in the absence of strong nucleophiles.[144] The tetrahedral mechanism in this case may be formulated as



$$R-\underset{\underset{O}{\|}}{C}-Cl + H_2O \rightleftharpoons R-\overset{\overset{\oplus}{OH_2}}{\underset{\underset{O^{\ominus}}{|}}{C}}-Cl \xrightarrow{-Cl^-} R-\underset{\underset{O}{\|}}{C}-\overset{\oplus}{O}H_2 \xrightleftharpoons{-H^+} R-\underset{\underset{O}{\|}}{C}-OH$$

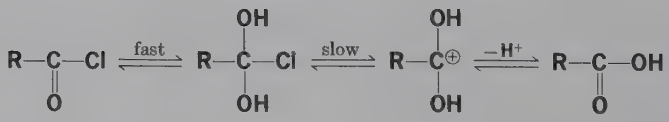
There are two possible paths for the S_N1 mechanism:

1.



$$R-\underset{\underset{O}{\|}}{C}-Cl \overset{\text{slow}}{\xrightleftharpoons{-Cl}} R-\underset{\underset{O}{\|}}{C}^{\oplus} \xrightarrow{H_2O} R-\underset{\underset{O}{\|}}{C}-\overset{\oplus}{O}H_2 \xrightarrow{-H^+} R-\underset{\underset{O}{\|}}{C}-OH$$

2.



$$R-\underset{\underset{O}{\|}}{C}-Cl \xrightleftharpoons{\text{fast}} R-\overset{\overset{OH}{|}}{\underset{\underset{OH}{|}}{C}}-Cl \xrightleftharpoons{\text{slow}} R-\overset{\overset{OH}{|}}{\underset{\underset{OH}{|}}{C}}^{\oplus} \xrightleftharpoons{-H^+} R-\underset{\underset{O}{\|}}{C}-OH$$

It is not easy to distinguish path 2 (which involves preliminary hydration) from path 1, but most evidence favors path 2.[145]

Hydrolysis of acyl halides is not usually catalyzed by acids, except for acyl fluorides, where hydrogen bonding can assist in the removal of F.[146]

OS **II,** 74.

---

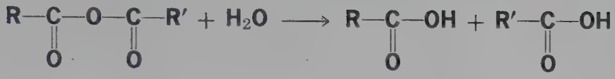
[142] Berti, Macchia, and Macchia, *Tetrahedron Letters* **1965,** 3421.

[143] For a review, see Sonntag, *Chem. Rev.* **52,** 237–416 (1953), pp. 251–258.

[144] Bender and Chen, *J. Am. Chem. Soc.* **85,** 30 (1963).

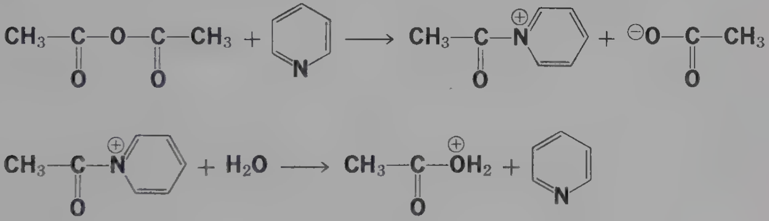
[145] Hudson and Moss, *J. Chem. Soc.* **1962,** 5157.

0-10 Hydrolysis of anhydrides



$$R-\underset{\underset{O}{\|}}{C}-O-\underset{\underset{O}{\|}}{C}-R' + H_2O \longrightarrow R-\underset{\underset{O}{\|}}{C}-OH + R'-\underset{\underset{O}{\|}}{C}-OH$$

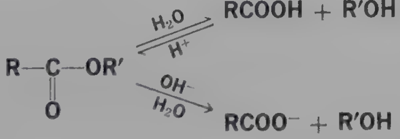
Anhydrides are somewhat more difficult to hydrolyze than acyl halides, but here too water is usually a strong enough nucleophile. The mechanism is usually tetrahedral. Only under acid catalysis does the S_N1 mechanism occur, and seldom even then.[147] Anhydride hydrolysis may also be catalyzed by bases. Of course, OH^- attacks more readily than water, but other bases can also catalyze the reaction. This phenomenon, called *nucleophilic catalysis* (p. 277), is actually the result of *two* successive tetrahedral mechanisms. For example, pyridine catalyzes the hydrolysis of acetic anhydride in this manner:[148]



Many other nucleophiles similarly catalyze the reaction.[66]

OS **I,** 408; **II,** 140, 368, 382; **IV,** 766; **40,** 71; **42,** 4.

0-11 Hydrolysis of esters



$$R-\underset{\underset{O}{\|}}{C}-OR' \quad \begin{matrix} \overset{H_2O}{\underset{H^+}{\rightleftharpoons}} RCOOH + R'OH \\ \xrightarrow[H_2O]{OH^-} RCOO^- + R'OH \end{matrix}$$

Ester hydrolysis is usually catalyzed by acids or bases. Since OR is a much poorer leaving group than halide or OCOR, water alone does not hydrolyze most esters. When bases catalyze the reaction, the attacking species is the more powerful nucleophile, OH^-. This reaction is called *saponification* and gives the salt of the acid. Acids catalyze the reaction by making the carbonyl carbon more positive so that the leaving group comes off more easily. Both reactions are equilibrium reactions, so that they are practicable only when there is a way of shifting the equilibrium to the right (as written). Since formation of the salt does just this, ester hydrolysis is almost always done for preparative purposes in basic solution, unless the compound is base-sensitive.

---

[146] Bevan and Hudson, *J. Chem. Soc.* **1953,** 2187; Satchell, *J. Chem. Soc.* **1963,** 555.

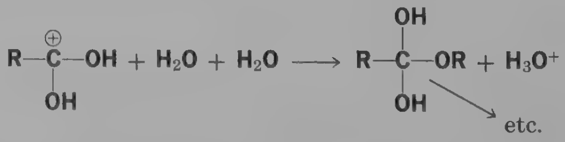
[147] Satchell, *Quart Rev.* (*London*) **17,** 160–203 (1963), pp. 172–173.

[148] Butler and Gold, *J. Chem. Soc.* **1961,** 4362.

Ester hydrolysis may also be catalyzed by metal ions, by enzymes, and by nucleophiles (see reaction **0-10**).[66] Methanesulfonic acid is also a good catalyst.[149] Phenolic esters may be similarly cleaved; in fact the reaction is usually faster for these compounds. Lactones also undergo the reaction, and thiol esters (RCOSR′) give mercaptans (R′SH).

Ingold[155] has classified the acid- or base-catalyzed hydrolysis of esters (and the formation of esters, since these are reversible reactions and thus have the same mechanisms) into eight possible mechanisms depending on the following conditions: (1) acid- or base-catalyzed, (2) unimolecular or bimolecular, and (3) acyl cleavage or alkyl cleavage. All eight of these are either S_N1, S_N2, or tetrahedral mechanisms. The acid-catalyzed mechanisms are shown with reversible arrows. They are not only reversible but symmetrical; that is, the mechanisms for ester formation are exactly the same as for hydrolysis except that H replaces R (Table 10). Internal proton transfers, such as shown for **37** and **38** and for **39** and **40**, may not actually be direct, but may take place through the solvent. The designations $A_{AC}1$, etc., are those of Ingold. The $A_{AC}2$ and $A_{AC}1$ mechanisms are also called A2 and A1, respectively. It may be noted that the $A_{AC}1$ mechanism is actually the same as the S_N1cA mechanism for this type of substrate, and that $A_{AL}2$ is analogous to S_N2cA. Some authors use A1 and A2 to refer to all types of nucleophilic substitution in which the leaving group first acquires a proton.

Of the eight mechanisms, only six have actually been observed. The two which have not been observed are the $B_{AC}1$ and the $A_{AL}2$ mechanisms. The $B_{AC}1$ is an S_N1 mechanism with OR′ as leaving group, which does not happen, while the $A_{AL}2$ requires water to be a nucleophile in an S_N2 process. The most common mechanisms are the $B_{AC}2$ for basic catalysis and the $A_{AC}2$[150] for acid catalysis, that is, the two tetrahedral mechanisms. Both of these involve acyl-oxygen cleavage. Evidence for this is (1) hydrolysis with $H_2{}^{18}O$ results in the ^{18}O appearing in the acid and not in the alcohol;[151] (2) esters with asymmetric R′ groups give alcohols with *retention* of configuration;[152] (3) allylic R′ gives no allylic rearrangement;[153] and (4) neopentyl R′ gives no rearrangement;[154] all of these facts indicating that the O—R′ bond is not broken. For the acid-catalyzed process the reaction is third order (first order each in substrate, water, and H^+), but this can be shown only when water is not the solvent. Martin has concluded that in the $A_{AC}2$ mechanism two molecules of water are required:



$$\mathrm{R-\underset{\displaystyle OH}{\overset{\oplus}{C}}-OH + H_2O + H_2O \longrightarrow R-\underset{\displaystyle OH}{\overset{\displaystyle OH}{C}}-OR + H_3O^+} \searrow \text{etc.}$$

---

[149] Loev, *Chem. Ind. (London)* **1964,** 193.

[150] For a discussion of this mechanism with specific attention to the proton transfers involved, see Zimmerman and Rudolph, *Angew. Chem. Intern. Ed. Engl.* **4,** 40–49 (1965).

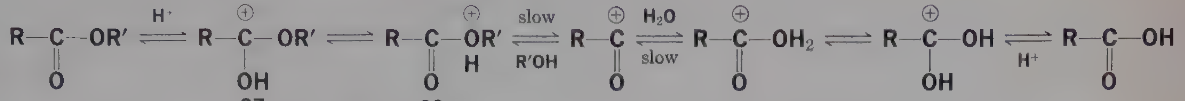
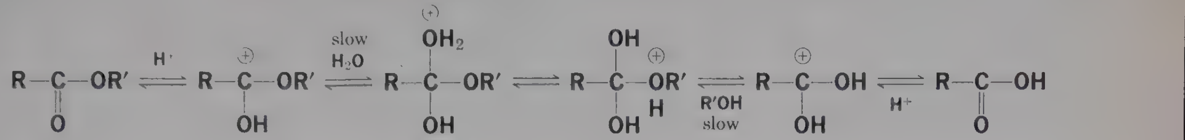
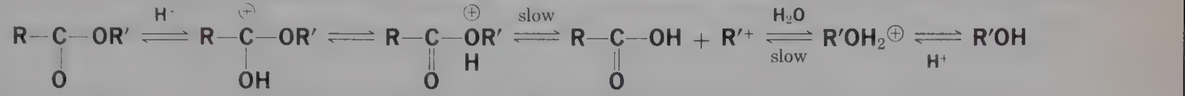
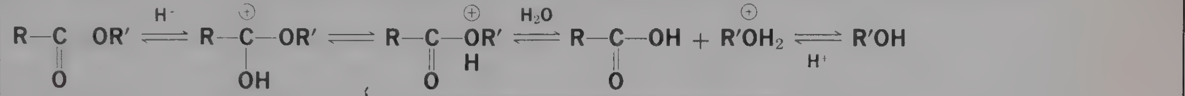
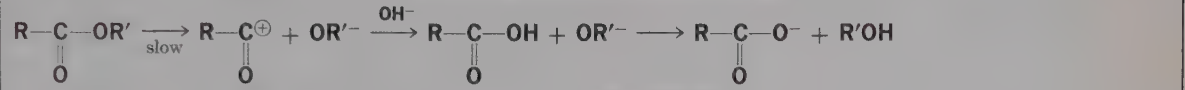
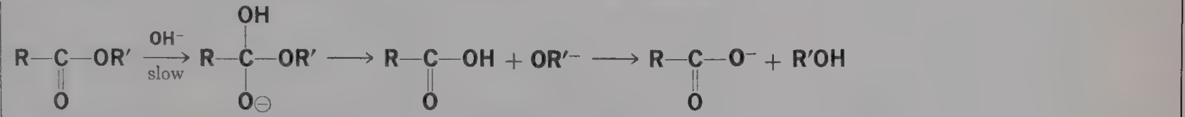
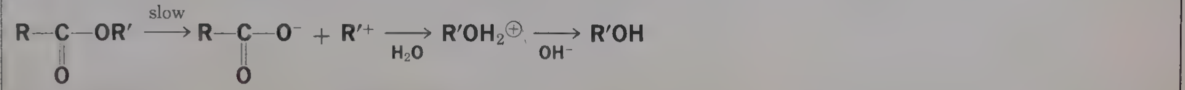
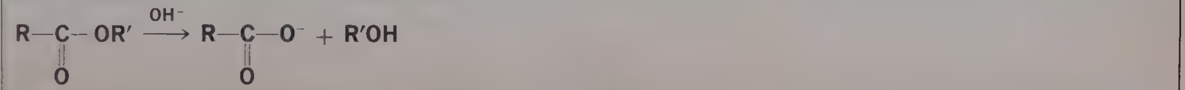
[151] For one of several examples, see Polanyi and Szabo, *Trans. Faraday Soc.* **30,** 508 (1934).

[152] Holmberg, *Ber.* **45,** 2997 (1912).

[153] Ingold and Ingold, *J. Chem. Soc.* **1932,** 758.

[154] Norton and Quayle, *J. Am. Chem. Soc.* **62,** 1170 (1940).

TABLE 10C. Classification of the eight possible mechanisms for ester hydrolysis and formation[155]

		Name	*Type*	
Acid catalysis	*acyl cleavage*	$A_{AC}1$	S_N1	 37 38
		$A_{AC}2$	Tetra-hedral	 39 40
	alkyl cleavage	$A_{AL}1$	S_N1	
		$A_{AL}2$	S_N2	
Basic catalysis	*acyl cleavage*	$B_{AC}1$	S_N1	
		$B_{AC}2$	Tetra-hedral	
	alkyl cleavage	$B_{AL}1$	S_N1	
		$B_{AL}2$	S_N2	

---

[155] Ingold, "Structure and Mechanism in Organic Chemistry," pp. 752–754, Cornell University Press, Ithaca, N.Y., 1953.

If this is so, the protonated derivatives **39** and **40** would not appear at all. This conclusion stems from a value of w (see p. 226) of about 5, indicating that water is acting as a proton donor here as well as a nucleophile.[156]

The other mechanism involving acyl cleavage is the $A_{AC}1$ mechanism. This is rare, being found only where R is very bulky, so that bimolecular attack is sterically hindered, and only in ionizing solvents. The mechanism has been demonstrated for esters of 2,4,6-trimethylbenzoic acid (mesitoic acid). This acid depresses the freezing point of sulfuric acid four times as much as would be predicted from its molecular weight, which is evidence for the equilibrium

$$\mathrm{ArCOOH + 2H_2SO_4 \rightleftharpoons ArCO^{\oplus} + H_3O^+ + 2HSO_4^-}$$

In a comparable solution of benzoic acid the freezing point is depressed only twice the predicted amount, indicating only a normal acid-base reaction. Further, a sulfuric acid solution of methyl mesitoate, when poured into water, gave mesitoic acid, while a similar solution of methyl benzoate, similarly treated, did not.[157]

The mechanisms involving alkyl-oxygen cleavage[158] are ordinary S_N1 and S_N2 mechanisms in which OCOR (an acyloxy group) or its conjugate acid is the leaving group. Two of the three mechanisms, the $B_{AL}1$ and $A_{AL}1$ mechanisms, occur most readily when R′ comes off as a stable carbonium ion, that is, when R′ is tertiary alkyl, allyl, benzyl, etc. For acid catalysis, nearly all esters with this type of alkyl group cleave by this mechanism,[159] but even for these substrates, the $B_{AL}1$ mechanism occurs only in neutral or weakly basic solution, where the rate of attack by OH^- is so slowed that the normally slow (by comparison) unimolecular cleavage takes over. These two mechanisms have been established by kinetic studies, ^{18}O labeling, and isomerization of R′.[160] The remaining mechanism, $B_{AL}2$, is very rare, but it has been observed in the hydrolysis of β-lactones,[161] the alkaline hydrolysis of methyl 2,4,6-tri-*tert*-butylbenzoate,[162] and in the unusual reaction[163]

$$\mathrm{ArCOOMe + RO^- \longrightarrow ArCOO^- + ROMe}$$

When it does occur, the $B_{AL}2$ mechanism is easy to detect, since it is the only one of the six observed mechanisms which requires inversion at R′. However, in the last example given, the mechanism is evident from the nature of the product, since the ether could have been formed in no other way.

To sum up the acid-catalysis mechanisms, $A_{AC}2$ and $A_{AL}1$ are the common mechanisms, the latter for R′ which give stable carbonium ions, the former for practically all the rest. $A_{AC}1$ is rare, being found only with strong acids and sterically hindered R. $A_{AL}2$ has not been observed. For basic catalysis, $B_{AC}2$ is almost universal; $B_{AL}1$ occurs only with R′ which give stable carbonium ions, and then only in weakly basic or neutral solution; $B_{AL}2$ is very rare; and $B_{AC}1$ has never been observed.

---

[156] Martin, *J. Am. Chem. Soc.* **84,** 4130 (1962).

[157] Treffers and Hammett, *J. Am. Chem. Soc.* **59,** 1708 (1937). For other evidence for this mechanism, see Bender and Chen, *J. Am. Chem. Soc.* **85,** 37 (1963).

[158] For a review of these, see Davies and Kenyon, *Quart. Rev. (London)* **9,** 203–228 (1955).

[159] For an exception, see Sandberg, *Acta Chem. Scand.* **16,** 1124 (1962), *Arkiv Kemi* **17,** 319 (1961).

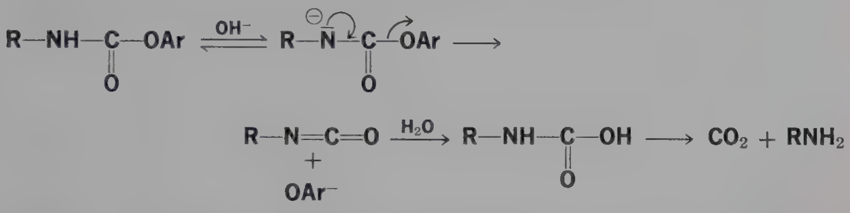
[160] For a discussion, see Ref. 155, pp. 779–782.

[161] Cowdrey, Hughes, Ingold, Masterman, and Scott, *J. Chem. Soc.* **1937,** 1264; Long and Purchase, *J. Am. Chem. Soc.* **73,** 3267 (1950).

[162] Barclay, Hall, and Cooke, *Can. J. Chem.* **40,** 1981 (1962).

[163] Sneen and Rosenberg, *J. Org. Chem.* **26,** 2099 (1961).

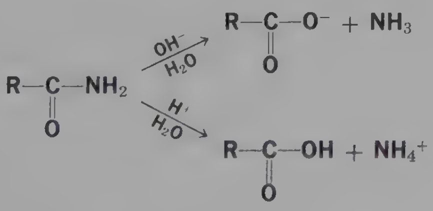
In the special case of alkaline hydrolysis of N-substituted aryl carbamates, there is another mechanism, involving elimination-addition:[164]



This mechanism does not apply to alkyl carbamates, or to unsubstituted or N,N-disubstituted aryl carbamates, all of which hydrolyze by the normal mechanisms.

OS **I**, 351, 360, 366, 379, 391, 418, 523; **II**, 1, 5, 53, 93, 194, 214, 258, 299, 416, 422, 474, 531, 549; **III**, 3, 33, 101, 209, 213, 234, 267, 272, 281, 300, 495, 510, 526, 531, 615, 637, 652, 705, 737, 774, 785, 809, 833, 835; **IV**, 15, 55, 169, 317, 417, 444, 532, 549, 555, 582, 590, 608, 616, 628, 630, 633, 635, 804; **40**, 85; **41**, 24, 60, 79; **42**, 4; **44**, 67. Ester hydrolyses with concomitant decarboxylation are listed at reaction **2-26** (p. 477).

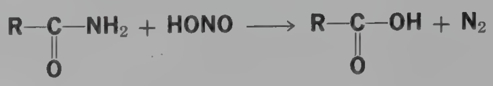
0-12 Hydrolysis of amides



Unsubstituted amides ($RCONH_2$) can be hydrolyzed with either acid or basic catalysis, the products being, respectively, the free acid and the ammonium ion, or the salt of the acid and ammonia. N-Substituted (RCONHR′) and N,N-disubstituted ($RCONR'_2$) amides can be hydrolyzed analogously, with the primary or secondary amine, respectively (or their salts), being obtained instead of ammonia. Lactams, imides, cyclic imides, hydrazides, etc., also undergo the reaction (see the Gabriel synthesis, **0-57**). Water alone is not sufficient to hydrolyze most amides, since NH_2 is even a poorer leaving group than OR. Often prolonged heating is required even with acid or basic catalysts. In difficult cases, nitrous acid may be used (unsubstituted amides only) in a reaction similar to **0-5:**

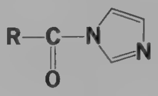
---

[164] Bender and Homer, *J. Org. Chem.* **30**, 3975 (1965).



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}NH_2 + HONO \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}OH + N_2}$$

In contrast to reaction **0-5**, side reactions are not a problem here, and this reaction is much faster than ordinary hydrolysis: for benzamide the rate ratio was 2.5×10^7.[165] Imidazolides (**41**) are particularly easy to hydrolyze,[166] and these are often used in synthesis (for an example, see p. 322).

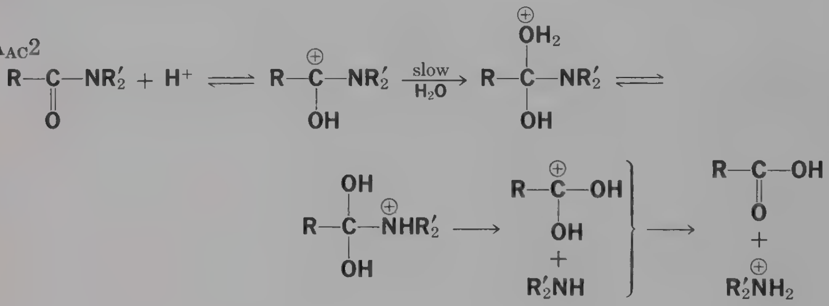


41

Similar compounds with more heterocyclic nitrogen atoms behave similarly.

These reactions are essentially irreversible for both acid and basic catalysis, since in both cases salts are formed. Just as in ester hydrolysis, the mechanism here is usually $\mathrm{A_{AC}2}$ or $\mathrm{B_{AC}2}$

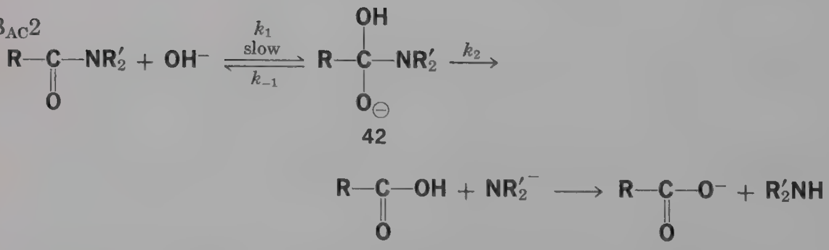
$\mathrm{A_{AC}2}$



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}NR'_2 + H^+ \rightleftharpoons R{-}\underset{\underset{OH}{|}}{\overset{\oplus}{C}}{-}NR'_2 \xrightarrow[H_2O]{slow} R{-}\underset{\underset{OH}{|}}{\overset{\overset{\oplus}{OH_2}}{\overset{|}{C}}}{-}NR'_2 \rightleftharpoons}$$

$$\mathrm{R{-}\underset{\underset{OH}{|}}{\overset{\overset{OH}{|}}{C}}{-}\overset{\oplus}{N}HR'_2 \longrightarrow \left.\begin{matrix} R{-}\overset{\oplus}{\underset{\underset{OH}{|}}{C}}{-}OH \\ + \\ R'_2NH \end{matrix}\right\} \longrightarrow \begin{matrix} R{-}\underset{\underset{O}{\|}}{C}{-}OH \\ + \\ R'_2\overset{\oplus}{N}H_2 \end{matrix}}$$

$\mathrm{B_{AC}2}$



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}NR'_2 + OH^- \underset{k_{-1}}{\overset{k_1}{\underset{slow}{\rightleftharpoons}}} \underset{\mathbf{42}}{R{-}\underset{\underset{O^{\ominus}}{|}}{\overset{\overset{OH}{|}}{C}}{-}NR'_2} \xrightarrow{k_2}}$$

$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}OH + NR_2'^{-} \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}O^- + R'_2NH}$$

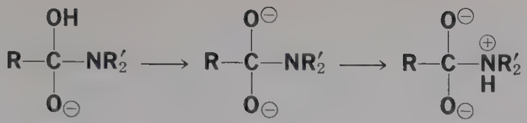
There is much evidence for these mechanisms, similar to that discussed for ester hydrolysis. In certain cases, kinetic studies on the basic hydrolysis has shown that the reaction is second order in OH^-, indicating that **42** can lose a proton to give **43**.[167]

---

[165] Ladenheim and Bender, *J. Am. Chem. Soc.* **82,** 1895 (1960).

[166] For a review, see Staab, *Angew. Chem. Intern. Ed. Engl.* **1,** 351–367 (1962).

[167] Biechler and Taft, *J. Am. Chem. Soc.* **79,** 4927 (1957).

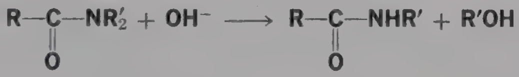


$$R-\overset{OH}{\underset{O^{\ominus}}{C}}-NR'_2 \longrightarrow R-\overset{O^{\ominus}}{\underset{O^{\ominus}}{C}}-NR'_2 \longrightarrow R-\overset{O^{\ominus}}{\underset{O^{\ominus}}{C}}-\underset{H}{\overset{\oplus}{N}}R'_2$$

42 43 44

Studies of the effect, on the ratio k_{-1}/k_2, of substituents in R′ led to the conclusion[168] that **43** adds a proton on the nitrogen before the nitrogen cleaves or, in other words, that NR_2 is not the leaving group, but *even in the base-catalyzed reaction,* the leaving group is its conjugate R'_2NH. This mechanism obviates the need for a final proton transfer as the last step of the basic-catalysis mechanism, since cleavage of **44** directly gives the products.

The four mechanisms involving alkyl—N cleavage (the AL mechanisms) do not apply to this reaction. They are not possible for unsubstituted amides, since the only N—C bond is the acyl bond. They are possible for N-substituted and N,N-disubstituted amides, but in these cases they give entirely different products and are not amide hydrolyses at all.



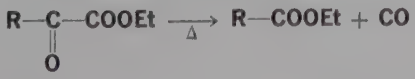
$$R-\underset{\displaystyle O}{\overset{}{\underset{\|}{C}}}-NR'_2 + OH^- \longrightarrow R-\underset{\displaystyle O}{\underset{\|}{C}}-NHR' + R'OH$$

This reaction, while rare, has been observed for various N-*tert*-butyl amides in 98% sulfuric acid, where the mechanism was the $A_{AL}1$ mechanism.[169] Of the remaining two acyl cleavage mechanisms, only the $A_{AC}1$ has been observed, in sulfuric acid solutions containing little free water.[170] Of course, the diazotization of unsubstituted amides might be expected to follow this mechanism, and there is evidence that this is true.[165]

OS **I,** 14, 111, 194, 201, 286; **II,** 19, 25, 28, 49, 76, 208, 330, 374, 384, 457, 462, 491, 503, 519, 612; **III,** 66, 88, 154, 256, 410, 456, 586, 591, 661, 735, 768, 813; **IV,** 39, 42, 55, 58, 420, 441, 496, 664; **40,** 18; **43,** 49; **44,** 44, 62.

0-13 Decarbonylation of esters and acids

$$Ar_3C-COOH \xrightarrow{H^+} Ar_3COH + CO$$



$$R-\underset{\displaystyle O}{\underset{\|}{C}}-COOEt \xrightarrow[\Delta]{} R-COOEt + CO$$

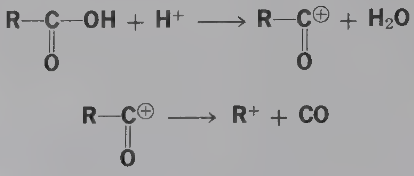
Decarbonylations of esters and acids are not general reactions. Only certain acids can be decarbonylated in this manner: formic, oxalic, triarylacetic, α-hydroxy, and α-keto acids. Most, but not all, α-keto esters may be decarbonylated simply by heating. The mechanisms are little known, and the reactions are included in this chapter because at least in some cases this mechanism has been demonstrated:[171]

---

[168] Bender and Thomas, *J. Am. Chem. Soc.* **83,** 4183 (1961).

[169] Lacey, *J. Chem. Soc.* **1960,** 1633.

[170] Duffy and Leisten, *J. Chem. Soc.* **1960,** 545, 853.



$$R-\underset{\underset{O}{\|}}{C}-OH + H^+ \longrightarrow R-\underset{\underset{O}{\|}}{C}^{\oplus} + H_2O$$

$$R-\underset{\underset{O}{\|}}{C}^{\oplus} \longrightarrow R^+ + CO$$

$$R^+ + H_2O \longrightarrow ROH + H^+$$

This is an S_N1 mechanism. The cleavage of the acyl cation is analogous to the cleavage of the diazonium ion RN_2^+.

OS **I,** 10; **II,** 279, 288, 531; **IV,** 141.

0-14 Oxidation of aldehydes to carboxylic acids. This reaction can proceed by a nucleophilic substitution mechanism, though more often it does not. It is considered in Chapter 14 (reaction **4-6,** p. 539).

0-15 Basic cleavage of β-keto esters and the haloform reaction could be considered at this point, but they are also electrophilic substitutions and are treated in that chapter (**2-29,** p. 481, and **2-30,** p. 482).

C. Attack by OR at an alkyl carbon

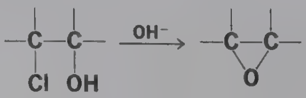
0-16 Alkylation with alkyl halides. The Williamson reaction

$$RX + OR'^- \longrightarrow ROR'$$

The *Williamson reaction,* discovered in 1850, is still the best general method for the preparation of unsymmetrical ethers or, for that matter, symmetrical ones. The reaction can also be carried out with aromatic R′, although C-alkylation is sometimes a side reaction (see p. 300). The method is not successful for tertiary R (because of elimination), and low yields are obtained with secondary R. Tertiary alkoxides react very slowly. Many other functional groups can be present in the molecule without interference. Active halides such as Ar_3CX may react directly with the alcohol without need for the more powerful nucleophile alkoxide ion. Even tertiary halides have been converted to ethers in this way, with no elimination.[172] *gem*-Dihalides react with alkoxides to give acetals, and 1,1,1-trihalides give ortho esters.

OS **I,** 75, 205, 258, 296, 435; **II,** 260; **III,** 127, 140, 209, 418, 432, 544; **IV,** 427, 457, 558, 590, 836; **40,** 29; **46,** 28.

0-17 Epoxide formation



---

[171] Ropp, *J. Am. Chem. Soc.* **82,** 842 (1960).

[172] Biordi and Moelwyn-Hughes, *J. Chem. Soc.* **1962,** 4291.

This is a special case of reaction **0-16**. Many epoxides have been made in this way. The method can also be used to prepare larger cyclic ethers: five- and six-membered rings. Additional treatment with base will yield the glycol (reaction **0-8**). The base pulls the proton from the OH group, and the epoxide then attacks in an internal S_N2 reaction. There is much evidence for this mechanism.[173]

OS **I**, 185, 233; **II**, 256; **III**, 835.

0-18 Alkylation with inorganic esters

$$R{-}OSO_2OR'' + R'O^- \longrightarrow ROR'$$

The reaction of alkyl sulfates with alkoxide ions is quite similar to reaction **0-16** in mechanism and scope. Other inorganic esters may also be used. However, the most common usage of this reaction is the formation of methyl esters of alcohols and phenols by treatment of alkoxides or aroxides with methyl sulfate. Organic esters sometimes give ethers when treated with alkoxides ($B_{AL}2$ mechanism, p. 312) in a very similar process (also see reaction **0-26**).

OS **I**, 58, 537; **II**, 387, 619; **III**, 127, 564, 800; **IV**, 588.

0-19 Alkylation with diazo compounds[174]

$$R_2CN_2 + ArOH \longrightarrow R_2CHOAr$$

$$CH_2N_2 + ROH \xrightarrow{HBF_4} CH_3OR$$

Reaction with alcohols is general for diazo compounds, but it is most often performed with diazomethane to produce methyl ethers, or with diazo ketones to produce α-keto ethers, since these kinds of diazo compounds are most readily available. With diazomethane the method is expensive and requires great caution. It is used chiefly to methylate alcohols and phenols which are expensive or available in small amounts, since the conditions are mild and high yields are obtained. Hydroxy compounds react better as their acidity increases, and ordinary alcohols do not react at all unless HBF_4[175] or $AlCl_3$[176] is present as a catalyst. The more acidic phenols react very well in the absence of a catalyst. Oximes, and ketones which have substantial enolic contributions, give O-alkylation. The mechanism is as in reaction **0-6**:

$$H_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{\underline{N}}| + ROH \longrightarrow H_3C{-}\overset{\oplus}{N}{\equiv}\underline{N} \longrightarrow H_3C^+ + RO^- \longrightarrow CH_3OR$$

OS **41**, 9. Also see OS **46**, 122.

0-20 Dehydration of alcohols

$$2ROH \xrightarrow{H_2SO_4} ROR + H_2O$$

---

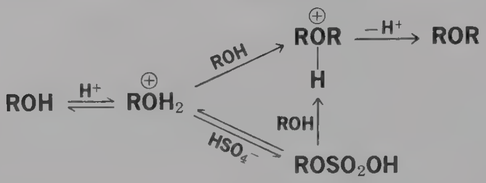
[173] Swain, Ketley, and Bader, *J. Am. Chem. Soc.* **81**, 2353 (1959).

[174] For a review, see Zollinger, "Azo and Diazo Chemistry," pp. 68–71, 102–108, Interscience Publishers, Inc., New York, 1961.

[175] Neeman, Caserio, Roberts, and Johnson, *Tetrahedron* **6**, 36 (1959).

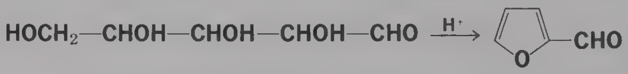
[176] Müller, Heischkeil, and Bauer, *Ann.* **677**, 55 (1964).

The dehydration of alcohols to form ethers is analogous to reactions **0-16** and **0-18**, but the species from which the leaving group departs is ROH_2^+ or $ROSO_2OH$. The former is obtained directly upon treatment of alcohols with sulfuric acid and may go, by an S_N1 or S_N2 pathway, directly to the ether if attacked by another molecule of alcohol. On the other hand, it may, again by either an S_N1 or S_N2 route, be attacked by the nucleophile HSO_4^-, in which case it is converted to $ROSO_2OH$, which in turn may be attacked by an alcohol molecule to give ROR. These processes are summarized:



Elimination is always a side reaction and, in the case of tertiary alkyl substrates, completely predominates.

The ether prepared is symmetrical. Mixed ethers can be prepared if one group is *tert*-butyl. Glycols can be converted to cyclic ethers, though the reaction is most successful for five-membered rings. Thus 1,6-hexanediol gives mostly 2-ethyltetrahydrofuran. This reaction is also important in preparing furfural derivatives from aldoses, with concurrent elimination:



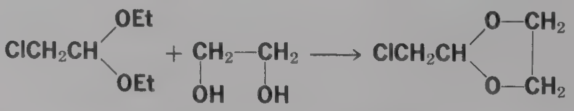
Phenols and primary alcohols form ethers when heated with dicyclohexylcarbodiimide[177] (see reaction **0-25**).

OS **I**, 280; **II**, 126; **IV**, 25, 72, 266, 350, 393, 534; **40**, 41, 88. Also see OS **46**, 60.

0-21 Transetherification

$$ROR' + R''OH \longrightarrow ROR'' + R'OH$$

The exchange of one alkoxyl group for another is very rare for *ethers*, though it has been accomplished with reactive R, for example, diphenylmethyl, with *p*-toluenesulfonic acid as a catalyst.[178] However, acetals and ortho esters undergo transetherification readily, for example,[179]



---

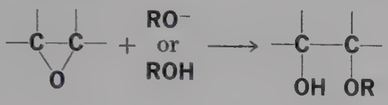
[177] Vowinkel, *Chem. Ber.* **95**, 2997 (1962), **96**, 1702 (1963); *Angew. Chem. Intern. Ed. Engl.* **2**, 218 (1963).

[178] Pratt and Draper, *J. Am. Chem. Soc.* **71**, 2846 (1949).

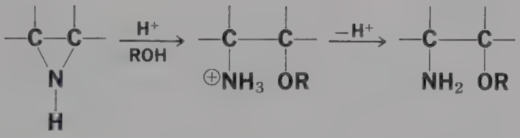
[179] Wagner and Zook, "Synthetic Organic Reactions," p. 265, John Wiley & Sons, Inc., New York, 1953.

There are no OS references, but see OS **46,** 113, 120 for somewhat similar reactions.

0-22 Alcoholysis of epoxides

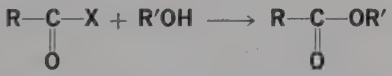


This reaction is analogous to reaction **0-8.** It may be acid- or base-catalyzed and may occur by either the S_N1 or S_N2 mechanisms. Many of the β-hydroxy ethers produced in this way are valuable solvents, for example, diethylene glycol, Cellosolve, etc. Aziridines may similarly be converted to β-amino ethers.[180]



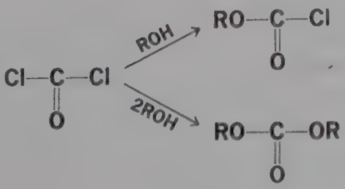
D. Attack by OR at an acyl carbon

0-23 Alcoholysis of acyl halides



$$R{-}\underset{\underset{O}{\|}}{C}{-}X + R'OH \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}OR'$$

The reaction between acyl halides and alcohols is the best general method for the preparation of esters.[181] The reaction is of wide scope, and many functional groups do not interfere. A base is frequently added to combine with the HX which is formed. When aqueous alkali is used, this is called the *Schotten-Baumann procedure,* but pyridine is also frequently used. Both R and R′ may be primary, secondary, or tertiary alkyl, or aryl. Enolic esters can also be prepared by this method, although C-acylation competes in these cases. When phosgene is the acyl halide, haloformic esters[182] or carbonates may be obtained.



---

[180] Harder, Pfeil, and Zenner, *Chem. Ber.* **97,** 510 (1964).

[181] For a review, see Sonntag, *Chem. Rev.* **52,** 237–416 (1953), pp. 312–324.

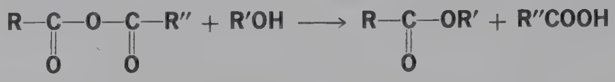
[182] For a review of this method as applied to the synthesis of chloroformates, see Matzner, Kurkjy, and Cotter, *Chem. Rev.* **64,** 645–687 (1964).

An important example is the preparation of carbobenzoxy chloride ($PhCH_2OCOCl$) from phosgene and benzyl alcohol. This compound is widely used for protection of amino groups during peptide synthesis.

As with reaction **0-9** the mechanism may be S_N1 or tetrahedral. Pyridine presumably catalyzes the reaction by the nucleophilic catalysis route (see reaction **0-10**).

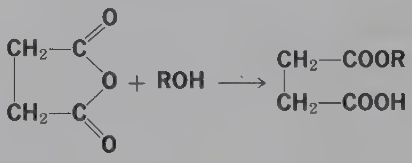
OS **I,** 12; **III,** 142, 144, 167, 187, 623, 714; **IV,** 84, 263, 478, 479, 608, 616, 788; **41,** 5; **44,** 20, 22; **46,** 1.

0-24 Alcoholysis of anhydrides



$$R-\underset{\underset{O}{\|}}{C}-O-\underset{\underset{O}{\|}}{C}-R'' + R'OH \longrightarrow R-\underset{\underset{O}{\|}}{C}-OR' + R''COOH$$

The scope of this reaction is similar to that of reaction **0-23.** Though anhydrides are somewhat less reactive than acyl halides, they are often used to prepare esters. Acids, Lewis acids, and bases are often used as catalysts—most often, pyridine. The catalysis is of the nucleophilic type; that is, there are two tetrahedral mechanisms (see p. 309). Cyclic anhydrides give mono-esterified dicarboxylic acids, for example,

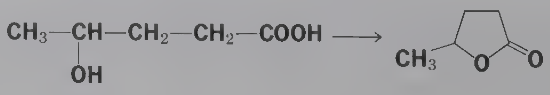


OS **I,** 285, 418; **II,** 69, 124; **III,** 11, 127, 141, 169, 237, 281, 428, 432, 452, 690, 833; **IV,** 15, 242, 304; **41,** 79; **42,** 4, 62; **43,** 27.

0-25 Esterification of acids

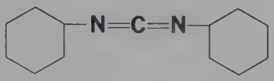
$$RCOOH + R'OH \overset{H^+}{\rightleftharpoons} RCOOR' + H_2O$$

The esterification of acids with alcohols is the reverse of reaction **0-12** and can be accomplished only if a means is available to drive the equilibrium to the right (as written). There are many ways of doing this, among which are (1) the addition of an excess of reactants, (2) the removal of the ester or the water by the distillation of an azeotropic mixture, and (3) the removal of water by the use of a dehydrating agent. R′ may be primary or secondary alkyl or aryl (phenolic esters), but tertiary alcohols usually give carbonium ions and elimination. γ- and δ-hydroxy acids are easily lactonized by treatment with acids, or sometimes simply on standing,

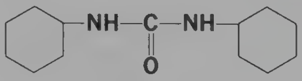


but larger and smaller lactone rings cannot be made in this manner, because polyester formation occurs more readily. However, sometimes the polyester can be converted to the lactone. Often the conversion of a group such as keto or halogen, γ or δ to a carboxyl group, to a hydroxyl group gives the lactone directly, since the hydroxy acid cyclizes too rapidly for isolation.

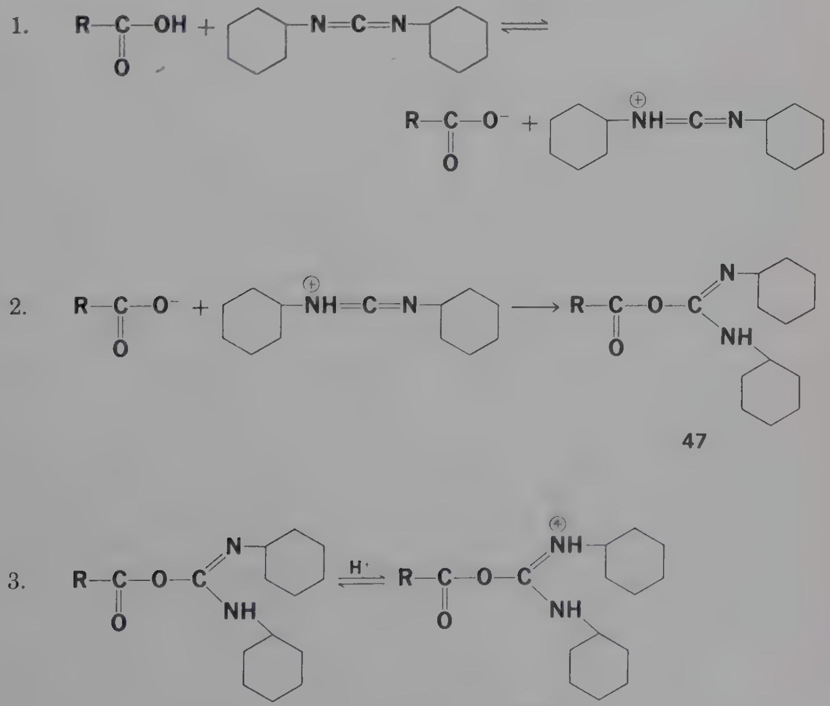
Esterification is catalyzed by acids (not bases) in ways that were discussed on page 310. The mechanisms are usually $A_{AC}2$, but $A_{AC}1$ and $A_{AL}1$ have also been observed. Esterification may also be promoted by the use of certain dehydrating agents. Among these is dicyclohexylcarbodiimide (**45**), which is converted in the process to dicyclohexylurea (**46**). The mechanism[183] has much in common with the nucleophilic catalysis mechanism: the acid is converted to a compound with a better leaving group. However, the conversion is not by a tetrahedral mechanism (as it is in nucleophilic catalysis), since the C—O bond remains intact during this step:



45



46



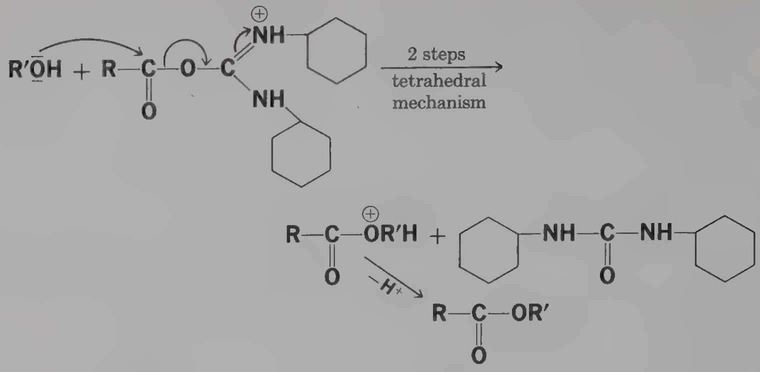
47

48

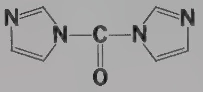
---

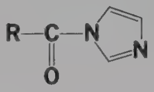
[183] Smith, Moffat, and Khorana, *J. Am. Chem. Soc.* **80**, 6204 (1958).

4.



Evidence for this mechanism was the preparation of O-acylureas similar to **47** and the finding that they react with alcohols, when catalyzed by acids, to give esters.[184] Other reagents which promote the reaction are trifluoroacetic anhydride[185] and N,N′-carbonyldiimidazole (**49**).[166] In the latter case,

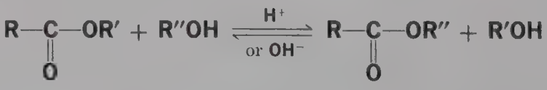

49


41

easily alcoholyzed imidazolides (**41**) are intermediates. BF_3 promotes the esterification by converting the acid to $RCO^+\ BF_3OH^-$, so that the reaction proceeds by an $A_{AC}1$ type of mechanism.

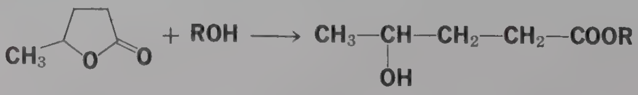
OS **I,** 42, 138, 237, 241, 246, 254, 261, 451; **II,** 260, 264, 276, 292, 365, 414, 526; **III,** 46, 203, 237, 381, 413, 526, 531, 610; **IV,** 169, 178, 302, 329, 390, 398, 427, 506, 532, 635, 677; **41,** 60; **43,** 3. Also see OS **III,** 536, 742; **IV,** 977.

0-26 Alcoholysis of esters. Transesterification



$$\mathrm{R{-}\underset{\|}{\overset{}{C}}{-}OR' + R''OH \underset{\text{or } OH^-}{\overset{H^+}{\rightleftharpoons}} R{-}C(=O){-}OR'' + R'OH}$$

This is an equilibrium reaction and must be shifted in the desired direction. In many cases low-boiling esters may be converted to higher ones by distillation of the lower-boiling alcohol as fast as it is formed. Lactones are easily opened by treatment with alcohols to give open-chain hydroxy esters:

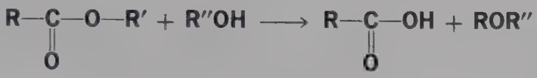


---

[184] Doleschall and Lempert, *Tetrahedron Letters* **1963**, 1195.

[185] Parish and Stock, *Tetrahedron Letters* **1964**, 1285.

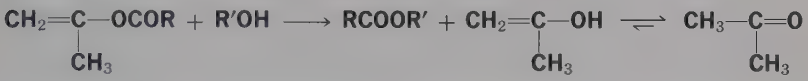
Transesterification occurs by mechanisms which are identical with those of ester hydrolysis—except that ROH replaces HOH—that is, by the acyl-oxygen fission mechanisms. When alkyl fission takes place, the products are the *acid* and the *ether:*



$$R-\underset{\underset{O}{\|}}{C}-O-R' + R''OH \longrightarrow R-\underset{\underset{O}{\|}}{C}-OH + ROR''$$

Therefore, transesterification reactions frequently fail when R′ is tertiary, since this type of substrate most often reacts by alkyl-oxygen cleavage. In such cases, the reaction is of the Williamson type with OCOR as the leaving group (see reaction **0-18**).

With enol esters, the free alcohol is the enol of a ketone, so such esters easily undergo the reaction



$$CH_2{=}\underset{\underset{CH_3}{|}}{C}-OCOR + R'OH \longrightarrow RCOOR' + CH_2{=}\underset{\underset{CH_3}{|}}{C}-OH \rightleftharpoons CH_3-\underset{\underset{CH_3}{|}}{C}{=}O$$

Hence, enol esters such as isopropenyl acetate are good acylating agents for alcohols.[186]

A closely related reaction is equilibration of a dicarboxylic acid and its diester to produce monoesters:

$$ROCO(CH_2)_nCOOR + HOOC(CH_2)_nCOOH \rightleftharpoons 2ROCO(CH_2)_nCOOH$$

OS **II,** 5, 122, 360; **III,** 123, 146, 165, 231, 281, 581, 605; **IV,** 10, 549, 630; **42,** 28.

Alcoholysis of amides is possible but is seldom performed, except for the imidazolide type of amide (p. 314).

E. Attack by OCOR at an alkyl carbon

0-27 Alkylation of acid salts

$$RX + R'COO^- \longrightarrow R'COOR$$

The preparation of esters by the treatment of alkyl halides with acid salts is usually useful only for fairly active R such as benzyl, allyl, etc., but not for tertiary alkyl, since elimination occurs instead. The salts used are often sodium, but silver salts or substituted ammonium salts[187] are also frequently used. This method (with Na^+, K^+, or Ag^+) is the best means of preparing trityl esters.[188] Lactones may be prepared from γ- and δ-halo acids by treatment with base (see reaction **0-25**).

---

[186] Jeffery and Satchell, *J. Chem. Soc.* **1962,** 1906.

[187] Merker and Scott, *J. Org. Chem.* **26,** 5180 (1961); Mills, Farrar, and Weinkauff, *Chem. Ind.* (*London*) **1962,** 2144.

[188] Berlin, Gower, White, Gibbs, and Sturm, *J. Org. Chem.* **27,** 3595 (1962).

The reaction may also be carried out with other leaving groups. Alkyl chlorosulfites (ROSOCl) and other derivatives of sulfuric and sulfonic acids may be treated with carboxylate ions to give the corresponding esters. When the substrate is an acetal of dimethylformamide, carboxylic acids are strong enough nucleophiles for the reaction:[189]

$$(RO)_2CHNMe_2 + R'COOH \longrightarrow R'COOR + ROH + HCONMe_2$$

This is an S_N2 process, since inversion is found at R.

OS **II,** 5; **III,** 650; **IV,** 582; **46,** 37.

0-28 Alkylation of acids with diazo compounds

$$R_2CN_2 + R'COOH \longrightarrow R'COOCHR_2$$

Acids may be converted to esters with diazo compounds in a reaction which is essentially the same as reaction **0-19.** In contrast to alcohols, carboxylic acids undergo the reaction quite well at room temperature, since the reactivity of the reagent increases with acidity. The reaction is used where high yields are important or where the acid is sensitive to higher temperatures. Because of availability, the diazo compounds most often used are diazomethane (for methyl esters)

$$CH_2N_2 + RCOOH \longrightarrow RCOOCH_3$$

and diazo ketones. The mechanism is as shown at reaction **0-19,** though in some cases at least, all three steps occur simultaneously, and there are no free RN_2^+ or R^+ intermediates.[190]

F. Attack by OCOR at an acyl carbon

0-29 Acylation of acids with acyl halides

$$RCOCl + R'COO^- \longrightarrow RCOOCOR'$$

Unsymmetrical as well as symmetrical anhydrides are often prepared by the treatment of an acyl halide with an acid salt. If a metallic salt is used, then Na^+, K^+, or Ag^+ are the most common cations, but more often pyridine or another tertiary amine is added to the free acid, and the salt thus formed is treated with the acyl halide. Anhydrides which are unaffected by cold water may be made in high yield by shaking an aqueous solution of the sodium salt of an acid with an acyl halide at room temperature in the presence of a tertiary amine.[191] Acyl halides may also be converted to anhydrides by treatment with esters (with a $ZnCl_2$ catalyst) or with anhydrides (an exchange reaction), but these methods are seldom used.

OS **III,** 28, 422, 488; **IV,** 285.

[189] Vorbrüggen, *Angew. Chem. Intern. Ed. Engl.* **2,** 211 (1963); Brechbühler, Büchi, Hatz, Schreiber, and Eschenmoser, *Angew. Chem. Intern. Ed. Engl.* **2,** 212 (1963).

[190] Roberts, Watanabe, and McMahon, *J. Am. Chem. Soc.* **73,** 760 (1951).

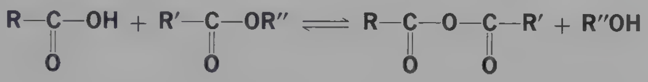
[191] Smalley and Suschitzky, *J. Chem. Soc.* **1964,** 755.

0-30 Acylation of acids with acids

$$2RCOOH \underset{}{\overset{P_2O_5}{\rightleftharpoons}} (RCO)_2O + H_2O$$

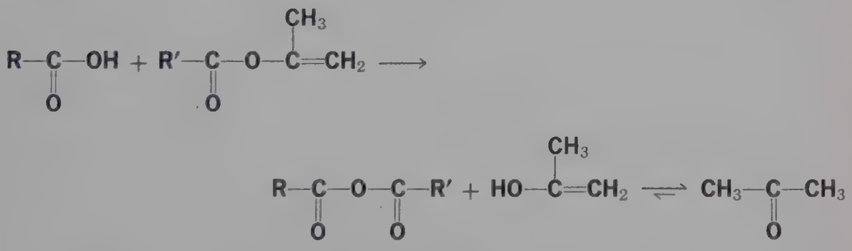
Anhydrides can be formed from two molecules of an ordinary acid only if a dehydrating agent is present so that the equilibrium can be driven to the right (as written). Common dehydrating agents are acetic anhydride and P_2O_5. However, diprotic acids which can form cyclic anhydrides of five-, six-, or seven-membered rings are converted to the anhydrides simply on heating. The method is very poor for the formation of mixed anhydrides.

Acids exchange with amides and esters, and these methods are sometimes used to prepare anhydrides if the equilibrium can be shifted; e.g.,



$$R-\underset{\substack{\| \\ O}}{C}-OH + R'-\underset{\substack{\| \\ O}}{C}-OR'' \rightleftharpoons R-\underset{\substack{\| \\ O}}{C}-O-\underset{\substack{\| \\ O}}{C}-R' + R''OH$$

Enolic esters are especially good for this purpose, since the equilibrium is shifted by formation of the ketone.



$$R-\underset{\substack{\| \\ O}}{C}-OH + R'-\underset{\substack{\| \\ O}}{C}-O-\overset{\substack{CH_3 \\ |}}{C}=CH_2 \longrightarrow$$

$$R-\underset{\substack{\| \\ O}}{C}-O-\underset{\substack{\| \\ O}}{C}-R' + HO-\overset{\substack{CH_3 \\ |}}{C}=CH_2 \rightleftharpoons CH_3-\underset{\substack{\| \\ O}}{C}-CH_3$$

Acids also exchange with anhydrides; indeed this is how acetic anhydride acts as a dehydrating agent in this reaction.

Anhydrides can be formed by treatment of the triethylammonium *salt* of a carboxylic acid with phosgene:[192]

$$2RCOO^{\ominus}\ \overset{\oplus}{N}HEt_3 \xrightarrow{COCl_2} RCOOCOR + 2\overset{\oplus}{N}HEt_3\ Cl^{\ominus} + CO_2$$

OS **I**, 91, 410; **II**, 194, 368, 560; **III**, 164, 449; **IV**, 242, 630, 790; **42**, 4.

G. **Other oxygen nucleophiles**

0-31 Preparation of peroxides and hydroperoxides

$$2RX + O_2^{=} \longrightarrow ROOR$$

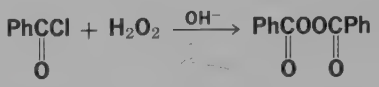
$$RX + OOH^{-} \longrightarrow ROOH$$

---

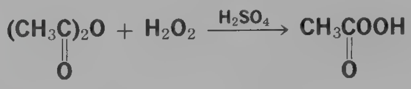
[192] Rinderknecht and Ma, *Helv. Chim. Acta* **47**, 152 (1964).

Hydroperoxides can be prepared by treatment of alkyl halides, esters of sulfuric or sulfonic acids, or alcohols with hydrogen peroxide in basic solution, where it is actually HO_2^-. Sodium peroxide is similarly used to prepare dialkyl peroxides. For R = benzyl, the reaction has been shown to proceed by the S_N1cB mechanism (p. 293), with phenylcarbene (PhCH) as an intermediate.[193]

Acyl peroxides and hydroperoxides can be similarly prepared, from acyl halides or anhydrides

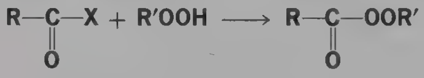


$$PhC(=O)Cl + H_2O_2 \xrightarrow{OH^-} PhC(=O)OOC(=O)Ph$$



$$(CH_3C(=O))_2O + H_2O_2 \xrightarrow{H_2SO_4} CH_3C(=O)OOH$$

and from amides of the imidazolide type (p. 314).[194] Diacyl peroxides can also be prepared by the treatment of carboxylic acids with hydrogen peroxide in the presence of dicyclohexylcarbodiimide (p. 321).[195] Mixed alkyl-acyl peroxides (peresters) can be made from acyl halides and hydroperoxides.



$$R{-}C(=O){-}X + R'OOH \longrightarrow R{-}C(=O){-}OOR'$$

OS **III**, 619, 649; **42**, 77; **43**, 93.

0-32 Preparation of inorganic esters

$$ROH + HONO_2 \xrightarrow{H^+} RONO_2$$

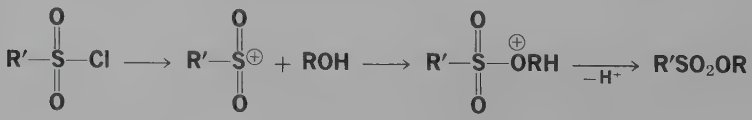
$$ROH + HONO \xrightarrow{H^+} RONO$$

$$ROH + SOCl_2 \longrightarrow ROSOOR$$

$$ROH + POCl_3 \longrightarrow PO(OR)_3$$

$$ROH + SO_3 \longrightarrow ROSO_2OH$$

The above reactions show a few of the many inorganic esters which may be prepared by attack of an inorganic acid or, better, its acid halide or anhydride, on an alcohol. Although for convenience all of these similar reactions are grouped together, the mechanism in many cases is not nucleophilic substitution at the alcoholic carbon. The other possible mechanism is nucleophilic substitution at the inorganic central atom:



$$R'{-}S(=O)_2{-}Cl \longrightarrow R'{-}S(=O)_2^{\oplus} + ROH \longrightarrow R'{-}S(=O)_2{-}\overset{\oplus}{O}RH \xrightarrow[-H^+]{} R'SO_2OR$$

---

[193] Pearson and Edgington, *J. Am. Chem. Soc.* **84**, 4607 (1962).

[194] Staab, Rohr, and Graf, *Chem. Ber.* **98**, 1122 (1965).

[195] Greene and Kazan, *J. Org. Chem.* **28**, 2168 (1963).

or a corresponding S_N2 type (see p. 372). In such cases there is no alkyl-O cleavage.

Alkyl halides are often used as substrates instead of alcohols. In such cases the *salt* of the inorganic acid is usually used, and the mechanism is nucleophilic substitution at the carbon atom. An important example is the treatment of alkyl halides with silver nitrate to form alkyl nitrates. This is often used as a test for alkyl halides. In some cases there is competition from the central atom. Thus nitrous acid is an ambident nucleophile which can give nitrites or nitro compounds. In some cases ethers may be substrates. Thus dialkyl or aryl alkyl ethers may be cleaved with anhydrous sulfonic acids:[196]

$$ROR' + R''SO_2OH \longrightarrow ROSO_2R'' + R'OH$$

R″ may be alkyl or aryl. For dialkyl ethers, the reaction does not end as indicated above, since R′OH is rapidly converted to R′OR′ by the sulfonic acid (reaction **0-20**), which in turn is further cleaved to $R'OSO_2R''$, so that the product is a mixture of the two sulfonates. For aryl alkyl ethers, cleavage always takes place to give the phenol, which is not converted to the ether under these conditions.

OS **II,** 106, 108, 109, 112, 204, 412; **III,** 148, 471; **IV,** 955; **43,** 83. Also see OS **II,** 111.

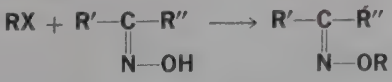
0-33 Preparation of mixed organic-inorganic anhydrides[197]

$$(RCO)_2O + HONO_2 \longrightarrow RCOONO_2$$

Mixed organic-inorganic anhydrides are seldom isolated, though they are often intermediates when acylation is carried out with acid derivatives catalyzed by inorganic acids. Sulfuric, perchloric, phosphoric, and other acids form similar anhydrides, most of which are unstable or not easily obtained because the equilibrium lies in the wrong direction. These intermediates are formed from amides, acids, and esters, as well as from anhydrides. Organic anhydrides of phosphoric acid are more stable than most others, and, for example, $RCOOPO(OH)_2$ may be prepared in the form of its salts.[198]

OS **I,** 495.

0-34 Alkylation of oximes



$$RX + R'-\underset{\underset{\displaystyle N-OH}{\|}}{C}-R'' \longrightarrow R'-\underset{\underset{\displaystyle N-OR}{\|}}{C}-R''$$

Oximes may be alkylated by alkyl halides or sulfates. N-Alkylation is a side reaction.

OS **III,** 172. Also see OS **42,** 30.

[196] Klamann and Weyerstahl, *Chem. Ber.* **98,** 2070 (1965).

[197] For a review, see Satchell, *Quart. Rev. (London)* **17,** 160–203 (1963), pp. 179–181.

[198] Avison, *J. Chem. Soc.* **1955,** 732.

0-35 Acylation at the oxygen of aldehydes (see reaction **6-55,** p. 716)

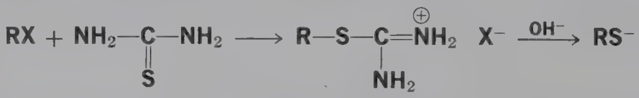
Sulfur Nucleophiles

0-36 Attack by SH at an alkyl carbon. Formation of mercaptans

$$\mathrm{RX + H_2S \longrightarrow RSH_2^+ \longrightarrow RSH + H^+}$$

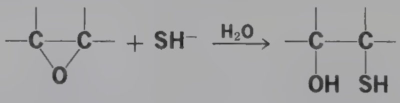
$$\mathrm{RX + HS^- \longrightarrow RSH}$$

Sodium sulfhydride (NaSH) is a much better reagent for the formation of mercaptans from alkyl halides than is H_2S, and is much more often used. It is easily prepared by bubbling H_2S into an alkaline solution. The reaction is most useful for primary halides. Secondary substrates give much lower yields, and the reaction fails completely for tertiary halides, because elimination predominates. Sulfuric and sulfonic esters may be used instead of halides. Sulfides (RSR) are often side products. An indirect method for the conversion of an alkyl halide to a mercaptan consists of treatment with thiourea to give an isothiuronium salt, which with alkali or a high-molecular-weight amine is cleaved to the mercaptan:



$$\mathrm{RX + NH_2{-}\underset{\underset{S}{\|}}{C}{-}NH_2 \longrightarrow R{-}S{-}\underset{\underset{NH_2}{|}}{C}{=}\overset{\oplus}{N}H_2\ \ X^- \xrightarrow{OH^-} RS^-}$$

Another indirect method is hydrolysis of Bunte salts (see reaction **0-40**). When epoxides are substrates, the products are β-hydroxy mercaptans:



OS **III,** 363, 440; **IV,** 401, 491; **42,** 100. Also see OS **II,** 345, 411, 573; **IV,** 232.

0-37 Attack by SR at an alkyl carbon. Formation of sulfides

$$\mathrm{RX + R'S^- \longrightarrow RSR'}$$

Sulfides may be prepared by treatment of alkyl halides with mercaptans. R′ may be alkyl or aryl. As in reaction **0-36,** RX cannot be a tertiary halide, and sulfuric and sulfonic esters can be used instead of halides. R may be tertiary if an alcohol is the substrate, e.g.,[199]

$$\mathrm{R_3COH + R'_3CSH \xrightarrow{H_2SO_4} R_3CSCR'_3}$$

This reaction is analogous to reaction **0-20.**

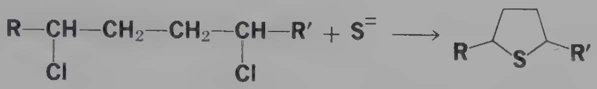
---

[199] Fehnel and Carmack, *J. Am. Chem. Soc.* **71,** 84 (1949); Cain, Evans, and Lee, *J. Chem. Soc.* **1962,** 1694.

Symmetrical sulfides may also be prepared by treatment of an alkyl halide with sodium sulfide.

$$2RX + Na_2S \longrightarrow RSR$$

This reaction may be carried out internally by addition of sulfide ions to 1,4- or 1,5-dihalides, to prepare five- and six-membered sulfur-containing heterocyclic rings.



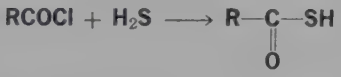
Selenides and tellurides may be prepared similarly.[200] When epoxides are substrates, β-hydroxy sulfides are obtained, in a manner analogous to that mentioned in reaction **0-36.**

Alkyl halides, treated with sulfides, give sulfonium salts.

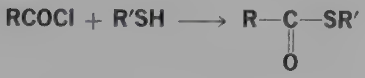
$$RCl + R'_2S \longrightarrow R'_2SR^+ \quad Cl^-$$

OS **II,** 31, 345, 547, 576; **III,** 332, 751, 763; **IV,** 396, 667, 892, 967; **42,** 59, 100.

0-38 Attack by SH or SR at an acyl carbon[201]



$$RCOCl + H_2S \longrightarrow R\underset{\underset{\displaystyle O}{\|}}{C}SH$$



$$RCOCl + R'SH \longrightarrow R\underset{\underset{\displaystyle O}{\|}}{C}SR'$$

Thiol acids and thiol esters may be prepared in this manner, which is analogous to reactions **0-9** and **0-26.** Anhydrides and aryl esters (RCOOAr) are also used as substrates, but the reagents in these cases are usually SH^- and SR^-.

OS **III,** 116, 599; **IV,** 924, 928.

0-39 Formation of disulfides

$$2RX + S_2^{=} \longrightarrow RSSR + 2X^-$$

Disulfides may be prepared by treatment of alkyl halides with disulfide ions and also indirectly by the reaction of Bunte salts (see reaction **0-40**) with acid solutions of iodide, thiocyanate ion, or thiourea,[202] or by pyrolysis, or treatment with hydrogen peroxide.

---

[200] Brandsma and Wijers, *Rec. trav. chim.* **82,** 68 (1963).

[201] For a review, see Ref. 197, pp. 182–184.

[202] Milligan and Swan, *J. Chem. Soc.* **1962,** 2172.

There are no OS references, but a similar preparation of a polysulfide may be found at OS **IV,** 295.

0-40 Formation of Bunte salts

$$\mathrm{RX} + \mathrm{S_2O_3^{=}} \longrightarrow \mathrm{R{-}S{-}SO_3^-} + \mathrm{X^-}$$

Alkyl halides are easily converted to Bunte salts ($\mathrm{RSSO_3^-}$) by treatment with thiosulfate ion. Bunte salts may be hydrolyzed with acids to give the corresponding mercaptans[203] or converted to disulfides, tetrasulfides, or pentasulfides.[204]

0-41 Alkylation of sulfinic acid salts

$$\mathrm{RX} + \mathrm{R'SO_2^-} \longrightarrow \mathrm{R{-}SO_2{-}R'} + \mathrm{X^-}$$

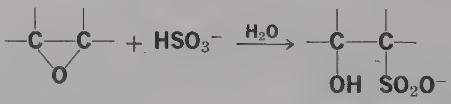
Alkyl halides or alkyl sulfates, treated with the salts of sulfinic acids, give sulfones.

OS **IV,** 674.

0-42 Attack by sulfite ion

$$\mathrm{RX} + \mathrm{SO_3^{=}} \longrightarrow \mathrm{R{-}SO_2O^-} + \mathrm{X^-}$$

Salts of sulfonic acids may be prepared by treatment of primary or secondary alkyl halides with sulfite ion.[204a] Even tertiary halides have been used, although the yields are low. Epoxides, treated with bisulfite, give β-hydroxy sulfonic acids:



OS **II,** 558, 564; **IV,** 529.

0-43 Formation of alkyl thiocyanates

$$\mathrm{RX} + \mathrm{SCN^-} \longrightarrow \mathrm{RSCN} + \mathrm{X^-}$$

Alkyl halides or sulfuric or sulfonic esters may be heated with sodium or potassium thiocyanate to give alkyl thiocyanates, although the attack by the analogous cyanate ion (reaction **0-61**) gives exclusive N-alkylation.

OS **II,** 366.

---

[203] Kice, *J. Org. Chem.* **28,** 957 (1963).

[204] Milligan, Saville, and Swan, *J. Chem. Soc.* **1963,** 3608.

[204a] For a review, see Gilbert, "Sulfonation and Related Reactions," pp. 136–148, 161–163, Interscience Publishers, Inc., New York, 1965.

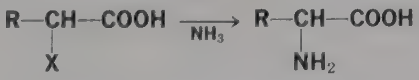
Nitrogen Nucleophiles

A. Attack by NH_2, NHR, or NR_2 at an alkyl carbon

0-44 Alkylation of amines

$$\begin{array}{llll}
3RX + NH_3 & \longrightarrow R_3N & + RX \longrightarrow & R_4N^+ \quad X^- \\
2RX + R'NH_2 & \longrightarrow R_2R'N & + RX \longrightarrow & R_3R'N^+ \quad X^- \\
RX + R'R''NH & \longrightarrow RR'R''N & + RX \longrightarrow & R_2R'R''N^+ \quad X^- \\
RX + R'R''R'''N & \longrightarrow RR'R''R'''N^+ \quad X^- & &
\end{array}$$

The reaction between alkyl halides and ammonia or primary amines is not usually a feasible method for the preparation of primary or secondary amines, since they are stronger bases than ammonia and preferentially attack the substrate. However, the reaction is very useful for the preparation of tertiary amines[205] and quaternary ammonium salts. If ammonia is the nucleophile, the three or four alkyl groups on the nitrogen of the product must be identical. If a primary, secondary, or tertiary amine is used, then different alkyl groups may be placed on the same nitrogen atom. The conversion of tertiary amines to quaternary salts is called the *Menschutkin reaction.* It is sometimes possible to use this method for the preparation of a primary amine, by the use of a large excess of ammonia, or of a secondary amine, by the use of a large excess of primary amine. However, the limitations of this approach may be seen in the reaction of a saturated solution of ammonia in 90% ethanol with ethyl bromide in a 16:1 molar ratio, under which conditions the yield of primary amine was 34.2% (at a 1:1 ratio the yield was 11.3%).[206] In some cases, where inductive or other effects cause the primary amine to be a weaker base than ammonia, it can easily be prepared in good yield. An important example is the conversion of α-halo acids to α-amino acids:



$$\underset{\displaystyle X}{R-\underset{|}{CH}-COOH} \xrightarrow[NH_3]{} \underset{\displaystyle NH_2}{R-\underset{|}{CH}-COOH}$$

Primary amines may be prepared from alkyl halides by method **0-45** or, more commonly, by the Gabriel synthesis (**0-57**).

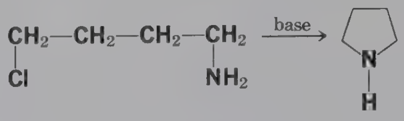
The conjugate bases of ammonia and of primary and secondary amines (NH_2^-, RNH^-, R_2N^-) are sometimes used as nucleophiles. However, they offer no advantages over ammonia or the amines themselves, since the latter are basic enough. This is in contrast to the analogous methods **0-1, 0-16, 0-36,** and **0-37.** Diaryl and triaryl amines are very poor nucleophiles, although the reaction has been carried out with diarylamines.[207] Sulfates or sulfonates may be used instead of halides. As usual, tertiary substrates do not give the reaction at all but undergo preferential elimination. The reaction may be carried out intramolecularly to give cyclic amines. Thus, 4-chloro-1-aminobutane treated with base gives pyrrolidine, and 2-chloroethylamine gives aziridine[208] (analogous to reaction **0-17**):

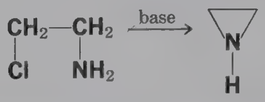
---

[205] For a review of this reaction with particular emphasis on the preparation of tertiary amines, see Spialter and Pappalardo, "The Acyclic Aliphatic Tertiary Amines," pp. 14–29, The Macmillan Company, New York, 1965.

[206] Werner, *J. Chem. Soc.* **113,** 899 (1918).

[207] Patai and Weiss, *J. Chem. Soc.* **1959,** 1035.





Phosphines behave similarly, and compounds of the type R_3P and $R_4P^+ \quad X^-$ may be so prepared.[209]

OS **I,** 23, 48, 102, 300, 488; **II,** 85, 183, 290, 328, 374, 397, 419, 563; **III,** 50, 148, 254, 256, 495, 504, 523, 705, 753, 774, 813, 848; **IV,** 84, 98, 383, 433, 466, 582, 585, 980; **40,** 31, 36, 66, 68, 85; **41,** 49; **42,** 19, 83; **44,** 7, 53, 72, 75, 86; **46,** 81. Also see OS **II,** 395; **IV,** 950.

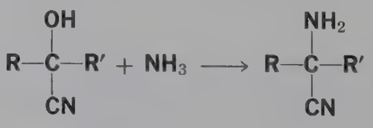
0-45 Conversion of alkyl halides to primary amines with hexamethylenetetramine

$$RX + (CH_2)_6N_4 \longrightarrow (CH_2)_6N_4 \cdot RX \xrightarrow{HCl} RNH_2$$

Primary amines may be prepared from alkyl halides by the use of hexamethylenetetramine. The method is most successful for primary bromides and iodides.

OS **43,** 6.

0-46 Replacement of a hydroxy by an amino group



$$R-\overset{\displaystyle OH}{\underset{\displaystyle CN}{C}}-R' + NH_3 \longrightarrow R-\overset{\displaystyle NH_2}{\underset{\displaystyle CN}{C}}-R'$$

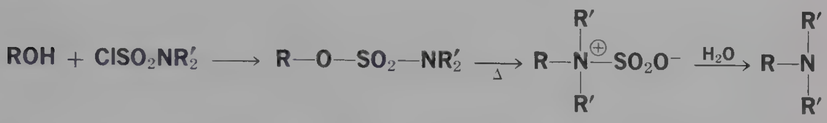
Cyanohydrins may be converted to amines by treatment with ammonia. Having a strong electron-withdrawing group α to a hydroxy group causes the latter to be a much better leaving group. In this case the presence of the cyano group enables the OH to leave as such without prior conversion to an ester or to its conjugate acid. The use of primary or secondary amines instead of ammonia leads to secondary and tertiary cyanoamines, respectively. It is more common to perform the conversion of an aldehyde or ketone directly to the cyanoamine without isolation of the cyanohydrin (see reaction **6-48,** p. 710).

---

[208] Closs and Brois, *J. Am. Chem. Soc.* **82,** 6068 (1960).

[209] Henderson and Buckler, *J. Am. Chem. Soc.* **82,** 5794 (1960).

Alcohols may be converted to amines in an indirect manner.[210] The salt of the alcohol is treated with a sulfamoyl chloride to give a sulfonamate ester, which on heating rearranges to a zwitterion. Hydrolysis of this gives the amine:



$$\mathrm{ROH} + \mathrm{ClSO_2NR'_2} \longrightarrow \mathrm{R{-}O{-}SO_2{-}NR'_2} \xrightarrow[\Delta]{} \mathrm{R{-}}\overset{\mathrm{R'}}{\underset{\mathrm{R'}}{\mathrm{N}^{\oplus}}}\mathrm{{-}SO_2O^-} \xrightarrow{\mathrm{H_2O}} \mathrm{R{-}}\overset{\mathrm{R'}}{\underset{\mathrm{R'}}{\mathrm{N}}}$$

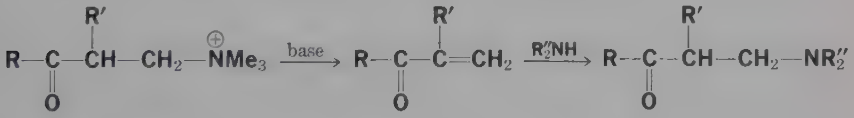
The reaction has been carried out with R' = methyl, to give tertiary amines, but there seems to be no reason why it will not be successful for R' = hydrogen as well, so that primary and secondary amines could also be prepared. The rearrangement step is an S_Ni process, as shown by retention of configuration at R. The success of the method increases with the stability of R^+ as a carbonium ion (compatible with the ion-pair nature of the S_Ni reaction, see p. 269). Therefore it is a particularly useful method for the preparation of tertiary alkyl amines, which are difficult to prepare in other ways.

OS **II**, 29, 231; **IV**, 91, 283. Also see OS **I**, 473; **III**, 272, 471.

0-47 Transamination

$$\mathrm{RNH_2} + \mathrm{R'NH^-} \longrightarrow \mathrm{RR'NH} + \mathrm{NH_2^-}$$

Where the nucleophile is the conjugate base of a primary amine, NH_2 can be a leaving group. The method has been used to prepare secondary amines.[211] Similar exchange, but with the attack by the amine itself, is observed with Mannich bases (see reaction **6-17**, p. 670), though the mechanism here is elimination-addition:[212]



$$\mathrm{R{-}}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{{-}}\overset{\mathrm{R'}}{\overset{|}{\mathrm{CH}}}\mathrm{{-}CH_2{-}}\overset{\oplus}{\mathrm{N}}\mathrm{Me_3} \xrightarrow{\text{base}} \mathrm{R{-}}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{{-}}\overset{\mathrm{R'}}{\overset{|}{\mathrm{C}}}\mathrm{{=}CH_2} \xrightarrow{\mathrm{R''_2NH}} \mathrm{R{-}}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{{-}}\overset{\mathrm{R'}}{\overset{|}{\mathrm{CH}}}\mathrm{{-}CH_2{-}NR''_2}$$

0-48 Alkylation of amines with diazo compounds

$$\mathrm{CR_2N_2} + \mathrm{R'_2NH} \xrightarrow{\mathrm{BF_3}} \mathrm{CHR_2NR'_2}$$

The reaction of diazo compounds with amines is similar to reaction **0-19.**[213] The acidity of amines is not great enough for the reaction to proceed without a catalyst, but BF_3, which converts the amine to the $F_3B\text{-}NHR'_2$ complex, enables the reaction to take place. As yet the method has been used exclusively or almost exclusively with diazomethane, so that this is a method for the methylation of amines. Ammonia has been used as the amine, but as in the case of reaction **0-44,** mixtures of primary, secondary, and tertiary amines are obtained. Primary aliphatic amines give mixtures of secondary and tertiary amines. Secondary amines give successful alkylation. Primary aromatic amines also give the reaction, but diaryl or arylalkylamines react very poorly.

---

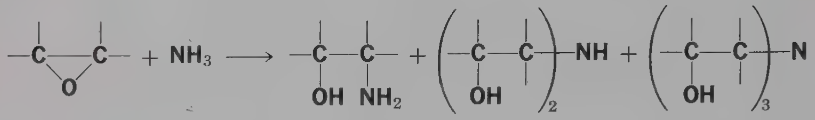
[210] White and Ellinger, *J. Am. Chem. Soc.* **87,** 5261 (1965).

[211] Baltzly and Blackman, *J. Org. Chem.* **28,** 1158 (1963).

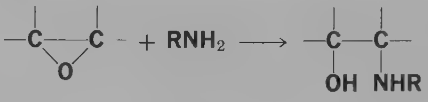
[212] See, for example, Casy and Myers, *J. Chem. Soc.* **1964,** 4639.

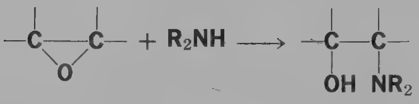
[213] Müller, Huber-Emden, and Rundel, *Ann.* **623,** 34 (1959).

0-49 Amination of epoxides



The reaction between epoxides and ammonia is a general and useful method for the preparation of β-hydroxyamines. Ammonia gives largely the primary amine, but also some secondary and tertiary amines. The useful solvents, the ethanolamines, are prepared by this reaction. Primary and secondary amines give, respectively, secondary and tertiary amines:





Episulfides, which can be generated *in situ* in various ways, react similarly to give β-amino mercaptans.[214]

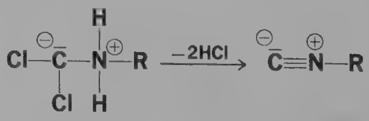
Triphenylphosphine similarly reacts with epoxides to give an intermediate which then undergoes elimination to give olefins (see the Wittig reaction, **6-45**, p. 702).

0-50 Formation of isonitriles

$$\mathrm{CHCl_3 + RNH_2 \xrightarrow{OH^-} R{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{\bar{C}}}$$

Reaction with chloroform under basic conditions is a common test for primary amines, since isonitriles have bad odors which are very strong. The reaction probably proceeds by an S_N1cB mechanism, with dichlorocarbene as an intermediate:

$$\mathrm{CHCl_3 + OH^- \longrightarrow \overset{\ominus}{\bar{C}}Cl_3 \xrightarrow{-Cl^-} CCl_2 + R\bar{N}H_2 \longrightarrow}$$



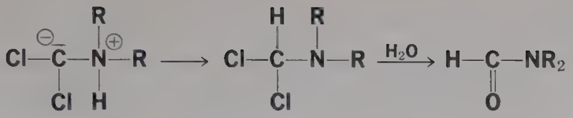
$$\mathrm{Cl{-}\underset{Cl}{\overset{\ominus}{\bar{C}}}{-}\underset{H}{\overset{H}{N^{\oplus}}}{-}R \xrightarrow{-2HCl} \overset{\ominus}{\bar{C}}{\equiv}\overset{\oplus}{N}{-}R}$$

When secondary amines are involved, the adduct cannot lose two moles of HCl. Instead it is hydrolyzed to an N,N-disubstituted formamide:[215]

---

[214] Reynolds, Massad, Fields, and Johnson, *J. Org. Chem.* **26**, 5109 (1961); Reynolds, Fields, and Johnson, *J. Org. Chem.* **26**, 5111, 5116, 5119, 5125 (1961); Wineman, Gollis, James, and Pomponi, *J. Org. Chem.* **27**, 4222 (1962).

[215] Saunders and Murray, *Tetrahedron* **6**, 88 (1959); Frankel, Feuer, and Bank, *Tetrahedron Letters* **1959**, No. 7, 5.



$$\mathrm{Cl{-}\underset{Cl}{\overset{\ominus}{C}}{-}\underset{H}{\overset{R}{N^{\oplus}}}{-}R \longrightarrow Cl{-}\underset{Cl}{\overset{H}{C}}{-}\overset{R}{N}{-}R \xrightarrow{H_2O} H{-}\underset{\overset{\|}{O}}{C}{-}NR_2}$$

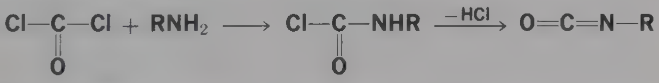
B. Attack by NH_2, NHR, or NR_2 at an acyl carbon

0-51 Acylation of amines by acyl halides

$$\mathrm{RCOX + NH_3 \longrightarrow RCONH_2 + HX}$$

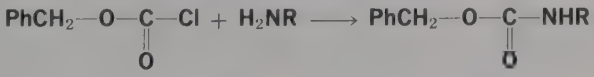
The treatment of acyl halides with ammonia or amines is a very general reaction for the preparation of amides.[216] Ammonia gives unsubstituted amides; primary amines give N-substituted amides; and secondary amines give N,N-disubstituted amides. Arylamines may be similarly acylated. In some cases aqueous alkali is added to combine with the liberated HCl. This is called the *Schotten-Baumann procedure,* as it was in reaction **0-23.**

Hydrazine and hydroxylamine also react with acyl halides to give, respectively, hydrazides, $RCONHNH_2$, and hydroxamic acids, RCONHOH, and these compounds are often made in this way. When phosgene is the acyl halide, primary amines at high temperatures give chloroformamides, ClCONHR, which lose HCl to give isocyanates, RNCO.



$$\mathrm{Cl{-}\underset{\overset{\|}{O}}{C}{-}Cl + RNH_2 \longrightarrow Cl{-}\underset{\overset{\|}{O}}{C}{-}NHR \xrightarrow{-HCl} O{=}C{=}N{-}R}$$

Thiophosgene, similarly treated, gives isothiocyanates. When chloroformates, ROCOCl, are treated with primary amines, carbamates, ROCONHR′, are obtained. An example of this reaction is the use of carbobenzoxy chloride to protect the amino group of amino acids and peptides:



$$\mathrm{PhCH_2{-}O{-}\underset{\overset{\|}{O}}{C}{-}Cl + H_2NR \longrightarrow PhCH_2{-}O{-}\underset{\overset{\|}{O}}{C}{-}NHR}$$

Amino groups in general are often protected by conversion to amides. The treatment of acyl halides with lithium nitride gives N,N-diacyl amides (triacylamines):[217]

$$\mathrm{3RCOCl + Li_3N \longrightarrow (RCO)_3N}$$

The nitrogen of dimethylformamide may also attack acyl halides, in what amounts to an exchange reaction:

$$\mathrm{RCOCl + HCONMe_2 \longrightarrow RCONMe_2 + [HCOCl] \longrightarrow HCl + CO}$$

The reactions proceed by the tetrahedral mechanism.[218]

OS **I,** 99, 165; **II,** 76, 208, 278, 328, 453; **III,** 167, 375, 415, 488, 490, 613; **IV,** 339, 411, 521, 620, 780.

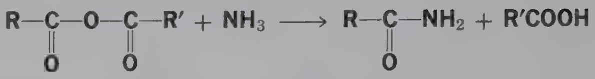
---

[216] For a review, see Sonntag, *Chem. Rev.* **52,** 237–416 (1953), pp. 258–294.

[217] Baldwin, Blanchard, and Koenig, *J. Org. Chem.* **30,** 671 (1965).

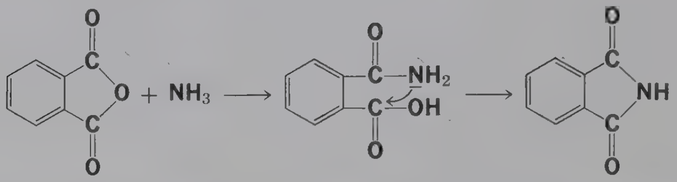
[218] Ref. 197, p. 185; Bender and Jones, *J. Org. Chem.* **27,** 3771 (1962).

0-52 Acylation of amines by anhydrides



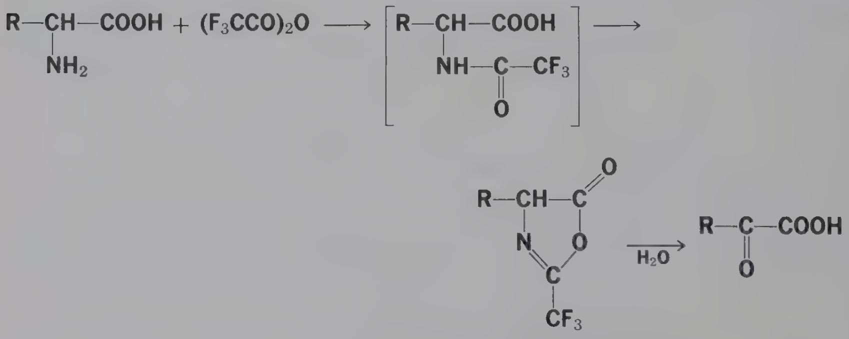
$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}O{-}\underset{\underset{O}{\|}}{C}{-}R' + NH_3 \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}NH_2 + R'COOH}$$

This reaction, similar in scope and mechanism to reaction **0-51**, may be carried out with ammonia, primary, or secondary amines. However, ammonia and primary amines may also give imides, in which two acyl groups are attached to the nitrogen. This is especially easy with cyclic anhydrides, which produce cyclic imides.



The second step in this case is the attack of the amide nitrogen on the carboxylic acid.

Even though formic anhydride is not a stable compound (see p. 416), amines may be formylated with a mixture of formic acid and acetic anhydride, which probably reacts as the mixed anhydride. When α-amino acids are treated with trifluoroacetic anhydride, the initial amide rapidly cyclizes, and hydrolysis of the product gives an α-keto acid.



This represents a method of converting α-amino acids to α-keto acids.[219]

OS **I**, 457; **II**, 11; **III**, 151, 456, 661, 813; **IV**, 5, 42, 106, 657; **40**, 21, 82; **41**, 93; **42**, 69.

0-53 Acylation of amines by acids

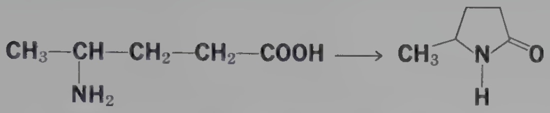
$$\mathrm{RCOOH + NH_3 \longrightarrow RCOO^-\ \ NH_4^+ \xrightarrow{pyrolysis} RCONH_2}$$

When carboxylic acids are treated with ammonia or amines, salts are obtained. The salts of ammonia, primary, or secondary amines may be pyrolyzed to give amides, but the method is less convenient than reactions **0-51**, **0-52**, and

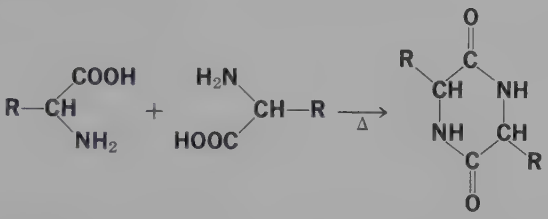
---

[219] Weygand, Steglich, and Tanner, *Ann.* **658**, 128 (1962).

0-54. Lactams are produced fairly easily from γ- or δ-amino acids, for example,

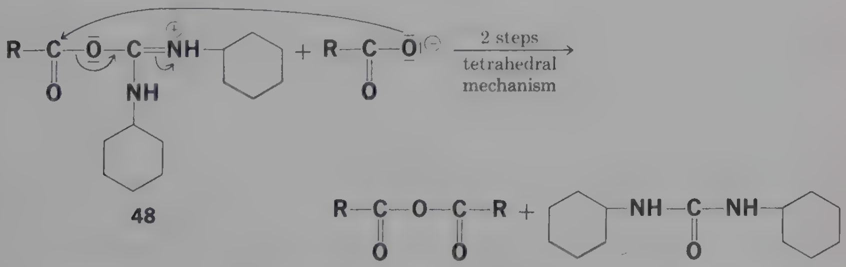


Upon heating, α-amino acids give diketopiperazines, an example of double amide formation:



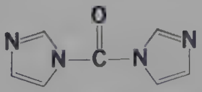
The details of the mechanism of this reaction are not clear, though it doubtless goes through a tetrahedral intermediate. For example, it is not known whether the salt or the small amount of free acid which is present is attacked by the amine.

Although treatment of acids with amines does not directly give amides, the reaction can be made to proceed in good yield at room temperature or slightly above, by the use of dehydrating agents, the most important of which is dicyclohexylcarbodiimide. This is very convenient and is used a great deal in peptide synthesis.[220] The mechanism is probably the same as in reaction **0-25** up to the formation of **48.** This intermediate is then attacked by another molecule of $RCOO^-$ to give the anhydride $(RCO)_2O$, which is the actual species which reacts with the amine:



48

The anhydride has been isolated from the reaction mixture and then used to acylate an amine.[221] Other promoting agents are N,N′-carbonyldiimidazole (**49**),[166] which behaves as in reaction **0-25** and has been used for peptide



49

---

[220] It was first used in this way by Sheehan and Hess, *J. Am. Chem. Soc.* **77**, 1067 (1955).

[221] Schüssler and Zahn, *Chem. Ber.* **95**, 1076 (1962).

synthesis,[222] and $POCl_3$.[223] Certain dicarboxylic acids form amides simply on treatment with primary aromatic amines. In these cases the cyclic anhydride is an intermediate and is the species actually attacked by the amine.[224] Acids can also be converted to amides by heating with amides of carboxylic acids (exchange), sulfonic acids, or phosphoric acids, for example,[225]

$$RCOOH + Ph_2PONH_2 \longrightarrow RCONH_2 + Ph_2POOH$$

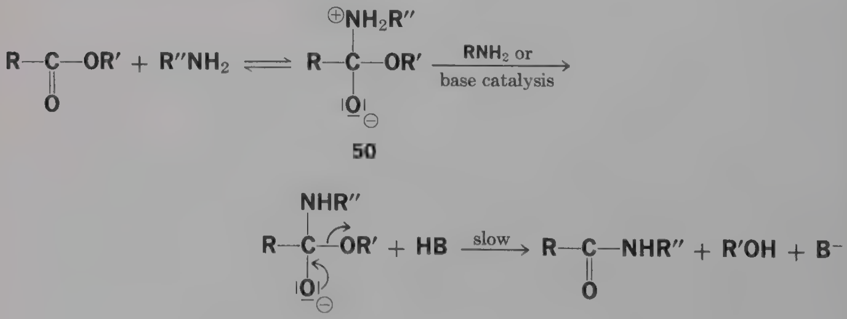
OS **I**, 3, 82, 111, 172, 327; **II**, 65, 562; **III**, 95, 328, 475, 590, 646, 656, 768; **IV**, 6, 62, 513; **40**, 99. Also see OS **III**, 360.

0-54 Acylation of amines by esters

$$RCOOR' + NH_3 \longrightarrow RCONH_2 + R'OH$$

The conversion of esters to amides is a useful reaction, and unsubstituted, N-substituted, and N,N-disubstituted amides may be prepared in this way from the appropriate amine. The reaction is particularly useful because many esters are readily available or easy to prepare even in cases where the corresponding acyl halide or anhydride is not. As in reaction **0-51**, hydrazides and hydroxamic acids may be prepared from esters, with hydrazine and hydroxylamine, respectively. Phenylhydrazides, prepared with phenylhydrazine, are often used as derivatives for esters, and the formation of hydroxamic acids is used as a test for esters. Lactones, when treated with ammonia or primary amines, give lactams. Lactams are also produced from γ- and δ-amino esters, in an internal example of this reaction. The basicity of some amines (for example, arylamines) is so low that the reaction goes with difficulty. However, when arylamines are converted to their conjugate bases $ArNH^-$, by a strong base such as ethoxide ion, the reaction proceeds at a convenient rate.[226]

The mechanism appears to be essentially $B_{AC}2$:[227]



$$R-\underset{\underset{O}{\|}}{C}-OR' + R''NH_2 \rightleftharpoons R-\overset{\overset{\oplus}{N}H_2R''}{\underset{|\underline{O}|^{\ominus}}{C}}-OR' \xrightarrow[\text{base catalysis}]{RNH_2 \text{ or}}$$

50

$$R-\overset{NHR''}{\underset{|\underline{O}|^{\ominus}}{C}}-OR' + HB \xrightarrow{\text{slow}} R-\underset{\underset{O}{\|}}{C}-NHR'' + R'OH + B^-$$

---

[222] Paul and Anderson, *J. Am. Chem. Soc.* **82**, 4596 (1960).

[223] Klosa, *J. prakt. Chem.* [4] **19**, 45 (1963).

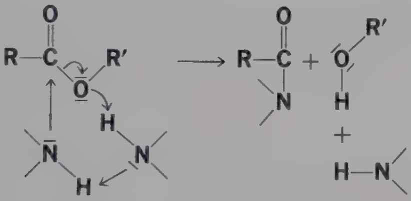
[224] Higuchi, Miki, Shah, and Herd, *J. Am. Chem. Soc.* **85**, 3655 (1963).

[225] Zhmurova, Voitsekhovskaya, and Kirsanov, *J. Gen. Chem. USSR* **29**, 2052 (1959).

[226] De Feo and Strickler, *J. Org. Chem.* **28**, 2915 (1963).

[227] Bunnett and Davis, *J. Am. Chem. Soc.* **82**, 665 (1960).

Evidence that the leaving group must be assisted by a proton donor (indicated above as HB) is that the rate is lower with NR_2^- in liquid ammonia, than with NHR_2 in water, apparently owing to the lack of acids to protonate the leaving oxygen. Also, the reaction is subject to both general acid and general base catalysis, indicating that proton transfer occurs in the slow step. In this case it can be shown that the presence of acid in the rate-determining step demands general base catalysis. It has been suggested[228] that the three steps occur simultaneously with a second molecule of ammonia or amine both pulling the proton from **50** as it is being formed and supplying a proton to the leaving group:



In this mechanism, the ammonia or amine is acting as an acid and a basic catalyst at the same time. It has been shown[229] that the reaction may proceed with alkyl-oxygen cleavage if there is sufficient steric hindrance in the ester. In this case, of course, the products are different:

$$RCOOR' + R''NH_2 \longrightarrow RCOOH + NHR'R''$$

This last reaction is similar to reaction **0-44,** with **OCOR** as the leaving group.

OS **I,** 153, 179; **II,** 67, 85; **III,** 10, 96, 108, 404, 440, 516, 536, 751, 765; **IV,** 80, 357, 441, 486, 532, 566, 819; **40,** 60; **44,** 22. Also see OS **I,** 5; **46,** 39.

0-55 Acylation of amines by amides

$$RCONH_2 + R'\overset{\oplus}{N}H_3 \longrightarrow RCONHR' + NH_4^+$$

This is an exchange reaction and is usually carried out with the salt of the amine. The leaving group is usually NH_2 rather than NHR or NR_2, and primary amines (in the form of their salts) are the most common reagents. BF_3 may be added to complex with the leaving ammonia.

OS **I,** 302 (but see **43,** 48), 450, 453; **II,** 461; **III,** 151, 404; **IV,** 361.

0-56 Acylation of amines by other acid derivatives. Acid derivatives which may be converted to amides include thiol acids RCOSH, thiol esters RCOSR, silicic esters $(RCOO)_4Si$, 1,1,1-trihalo ketones $RCOCX_3$; and nonenolizable ketones (see the Haller-Bauer reaction **2-32,** p. 483).

OS **III,** 394; **IV,** 6, 569; **44,** 18, 20.

---

[228] Bruice and Mayahi, *J. Am. Chem. Soc.* **82,** 3067 (1960).

[229] Zaugg, Helgren, and Schaefer, *J. Org. Chem.* **28,** 2617 (1963).

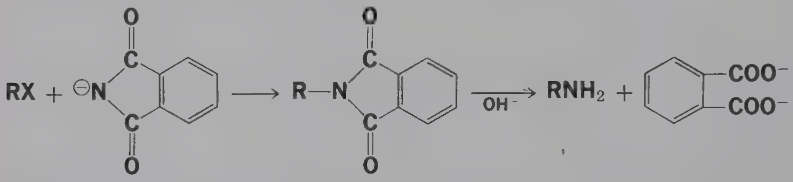
C. Attack by NHCOR

0-57 N-Alkylation of amides and imides

$$\mathrm{RX} + {}^{\ominus}\mathrm{NHCOR'} \longrightarrow \mathrm{RNHCOR'}$$

Amides are very weak bases; far too weak to attack alkyl halides, so that they must first be converted to their salts. By this method, unsubstituted amides may be converted to N-substituted, or N-substituted to N,N-disubstituted, amides. Esters of sulfuric or sulfonic acids may also be substrates. Tertiary substrates give elimination. O-Alkylation is at times a side reaction.

The *Gabriel synthesis,* for converting halides to primary amines, is based on this reaction. The halide is treated with potassium phthalimide and the product hydrolyzed (reaction **0-12**):



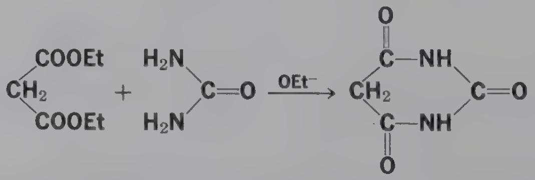
Amides may also be alkylated with diazo compounds, as in reaction **0-48.** Salts of sulfonamides ($\mathrm{ArSO_2NH^-}$) may be used to attack alkyl halides to prepare N-alkyl sulfonamides ($\mathrm{ArSO_2NHR}$).

OS **I,** 119, 203, 271; **II,** 25, 83, 208; **III,** 151; **IV,** 810.

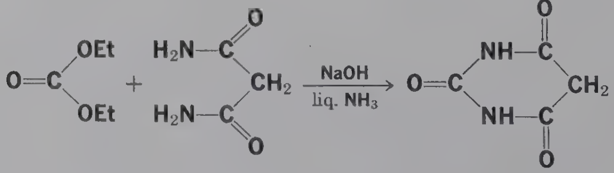
0-58 N-Acylation of amides and imides

$$\mathrm{RCOCl} + \mathrm{H_2NCOR'} \longrightarrow \mathrm{RCONHCOR'}$$

Imides may be prepared by the attack of amides or their salts upon acyl halides, anhydrides, esters, or acids. The reaction is most often used to prepare urea derivatives, an important example being the preparation of barbituric acid:



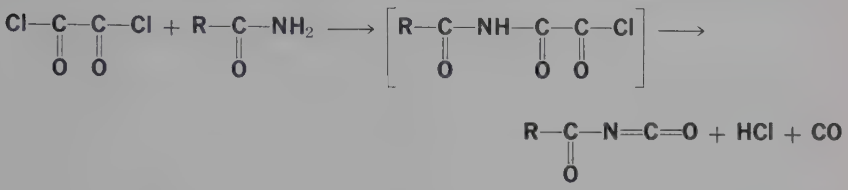
It is also possible to prepare this compound in the reverse manner:[230]



---

[230] Shimo and Wakamatsu, *J. Org. Chem.* **24,** 19 (1959).

When the substrate is oxalyl chloride (ClCOCOCl) and the reagent an unsubstituted amide, an acyl isocyanate is formed. The "normal" product (RCONHCOCOCl) does not form, or if it does, it rapidly loses CO and HCl:[231]



$$\mathrm{Cl{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{O}{\|}}{C}{-}Cl + R{-}\underset{\underset{O}{\|}}{C}{-}NH_2 \longrightarrow \left[R{-}\underset{\underset{O}{\|}}{C}{-}NH{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{O}{\|}}{C}{-}Cl\right] \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}N{=}C{=}O + HCl + CO}$$

OS **II**, 60, 79, 422; **III**, 763; **IV**, 245, 247, 496, 566, 638, 662, 744; **41**, 93; **46**, 16.

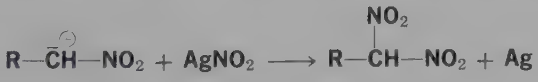
D. Other nitrogen nucleophiles

0-59 Formation of nitro compounds[232]

$$\mathrm{RX + NO_2^- \longrightarrow RNO_2}$$

Sodium nitrite may be used to form nitro compounds with primary or secondary alkyl bromides or iodides. Silver nitrite gives nitro compounds only when RX is a primary bromide or iodide. Nitrite esters are an important side product in all these cases (reaction **0-32**) and become the major product when secondary or tertiary halides are treated with silver nitrite.

gem-Dinitro compounds may be prepared in a way which is not a nucleophilic substitution, from silver nitrite and salts of nitro compounds:[233]



$$\mathrm{R{-}\overset{\ominus}{\bar{C}}H{-}NO_2 + AgNO_2 \longrightarrow R{-}\overset{\overset{NO_2}{|}}{C}H{-}NO_2 + Ag}$$

This is an oxidation-reduction reaction.

OS **I**, 401; **IV**, 368, 454, 724.

0-60 Formation of azides

$$\mathrm{RX + N_3^- \longrightarrow RN_3}$$

$$\mathrm{RCOX + N_3^- \longrightarrow RCON_3}$$

Both alkyl and acyl azides may be formed by treatment of the appropriate halide with sodium azide.[234] Acyl azides, which can be used in the Curtius reaction (**8-16**, p. 818), may also be formed from anhydrides.

OS **III**, 846; **IV**, 715.

---

[231] Speziale and Smith, *J. Org. Chem.* **27**, 3742 (1962); Speziale, Smith, and Fedder, *J. Org. Chem.* **30**, 4306 (1965).

[232] For a review, see Kornblum, *Org. Reactions* **12**, 101–156 (1962).

[233] Kaplan and Shechter, *J. Am. Chem. Soc.* **83**, 3535 (1961).

[234] For a review, see Boyer and Canter, *Chem. Rev.* **54**, 1–57 (1954).

0-61 Formation of isocyanates and isothiocyanates

$$RX + NCO^- \longrightarrow RNCO$$
$$RX + NCS^- \longrightarrow RNCS$$

When the reagent is the thiocyanate ion, S-alkylation is an important side reaction (**0-43**), but the cyanate ion gives exclusive N-alkylation. When alkyl halides are treated with NCO^- in the presence of ethanol, urethans may be prepared directly (see reaction **6-8**, p. 663).[235] Acyl halides give the corresponding acyl isocyanates and isothiocyanates. For the formation of isocyanides, see reaction **0-88.**

OS **III**, 735; **44**, 91.

Halogen Nucleophiles

A. Attack at an alkyl carbon

0-62 Halide exchange. The Finkelstein reaction

$$RX + X'^- \rightleftharpoons RX' + X^-$$

Halide exchange, sometimes called the *Finkelstein reaction,* is an equilibrium process, but it is often possible to shift the equilibrium. The reaction is most often applied to the preparation of iodides and fluorides. Iodides may be prepared from chlorides or bromides by taking advantage of the fact that sodium iodide, but not the bromide or chloride, is soluble in acetone. When an alkyl chloride or bromide is treated with a solution of sodium iodide in acetone, the equilibrium is shifted by the precipitation of sodium chloride or bromide. This is thus a method for the preparation of alkyl iodides. Since the mechanism is S_N2, the reaction is much more successful for primary halides than for secondary or tertiary halides, and sodium iodide in acetone is often used as a test for primary bromides or chlorides. Fluorides are prepared by treatment of other alkyl halides with any of a number of fluorinating agents, among them KF, AgF, HgF_2, and for polyhalo compounds (such as chloroform), HF plus SbF_3.[236] The equilibria in these cases are shifted because the alkyl fluoride, once formed, has little tendency to react, owing to the extremely poor leaving-group ability of fluorine.

Not only can one halogen be substituted for another, but the halogen exchange reaction can also be carried out with, say, radioactive chloride replacing chloride, for studying mechanisms (see p. 255). Alkyl halides also exchange with *halogens* (X_2 rather than X^-). This is a free-radical reaction.[237]

---

[235] Argabright, Rider, and Sieck, *J. Org. Chem.* **30,** 3317 (1965).

[236] A discussion of the use of these reagents will be found in the review articles: Stephens and Tatlow, *Quart. Rev. (London)* **16,** 44–70 (1962); Henne, *Org. Reactions* **2,** 49–93 (1944); Bockemüller, in "Newer Methods of Preparative Organic Chemistry," vol. 1, pp. 235–245, Interscience Publishers, Inc., New York, 1948.

[237] Gazith and Noyes, *J. Am. Chem. Soc.* **77,** 6091 (1955); Gardner and Noyes, *J. Am. Chem. Soc.* **83,** 2409 (1961); Miller, Neiman, and Solovnikov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1959,** 227.

Acyl fluorides may be prepared by treating acyl chlorides with sodium fluoride and hydrofluoric acid. Other acyl halide interchange has also been accomplished, although seldom. When it is done, it is always acyl iodides and bromides that are made from chlorides, since the chlorides are by far the most readily available.

OS **II**, 476; **IV**, 84, 525.

0-63 Formation of alkyl halides from esters of sulfuric and sulfonic acids

$$ROSO_2R' + X^- \longrightarrow RX$$

Alkyl sulfates, tosylates, and other esters of sulfuric and sulfonic acids may be converted to alkyl halides with any of the four halide ions. Inorganic esters are intermediates in the conversion of alcohols to alkyl halides with $SOCl_2$, PCl_5, PCl_3, etc. (reaction **0-64**), but are seldom isolated.

OS **I**, 25; **II**, 111, 404; **IV**, 597, 753.

0-64 Formation of alkyl halides from alcohols

$$ROH + HX \longrightarrow RX$$

$$ROH + SOCl_2 \longrightarrow RCl$$

Alcohols may be converted to alkyl halides with several reagents, the most common of which are halogen acids HX and inorganic acid halides such as $SOCl_2$, PCl_5, PCl_3, $POCl_3$, etc. HBr is usually used for alkyl bromides and HI for alkyl iodides. These reagents are often generated *in situ* from the halide ion and an acid such as phosphoric or sulfuric. The use of HI sometimes results in reduction of the alkyl iodide to the alkane (reaction **0-73**). The reaction may be used to prepare primary, secondary, or tertiary halides, but alcohols of the isobutyl or neopentyl types often give large amounts of rearrangement products. Tertiary chlorides are easily made with concentrated HCl, but primary and secondary alcohols react with HCl so slowly that a catalyst, usually zinc chloride, is required. This behavior is the basis of the *Lucas test* for distinguishing among primary, secondary, and tertiary alcohols. The test consists of shaking the alcohol with a mixture of concentrated HCl and zinc chloride at room temperature. Tertiary alcohols react at once, secondary alcohols within five minutes, and primary alcohols do not react within this time. The inorganic acid chlorides $SOCl_2$, PCl_3, etc., give primary, secondary, or tertiary alkyl chlorides with much less rearrangement than is observed with HCl, and these reagents are often preferred for the preparation of chlorides. Analogous bromides and iodides, especially PBr_3, have also been used, but they are more expensive and less often used than HBr or HI, although some of them, too, may be generated *in situ*. Secondary alcohols always give *some* rearranged bromides if another secondary position is available, even with PBr_3, PBr_5, or $SOBr_2$; thus 3-pentanol gives both 2- and 3-bromopentane. Such rearrangement may be avoided by converting the alcohol to a sulfonate and then using reaction **0-63**.[238] However, this is not necessary for secondary *chlorides,* since $SOCl_2$ gives no rearrangement. HF does not convert alcohols to alkyl fluorides. Such conversions can be carried out with SF_4,[239] with α-fluoroamines of the type $R'CF_2NR''_2$,[240] or indirectly.

---

[238] Cason and Correia, *J. Org. Chem.* **26**, 3645 (1961).

Other reagents have also been used, for example, $(RO)_3PRX$ and R_3PX_2,[241] which give good yields of primary, secondary, and tertiary halides without rearrangements, and $Cl_2C{=}CClNEt_2$.[242]

When the reagent is HX, the mechanism is S_N1cA or S_N2cA: that is, the leaving group is not OH^-, but OH_2 (p. 290). The leaving group is not OH^- with the other reagents either, since in these cases the alcohol is first converted to an inorganic ester, for example, ROSOCl with $SOCl_2$ (reaction **0-32**). The leaving group is therefore $OSOCl^-$ or a similar group (reaction **0-63**). These may react by the S_N1 or S_N2 mechanism and, in the case of ROSOCl, by the S_Ni mechanism.

OS **I,** 25, 36, 131, 142, 144, 292, 294, 533; **II,** 91, 136, 159, 246, 308, 322, 358, 399, 476; **III,** 11, 227, 370, 446, 698, 793, 841; **IV,** 106, 169, 323, 333, 576, 681; **41,** 49; **46,** 1. Also see OS **III,** 818; **IV,** 278, 383, 597.

0-65 Cleavage of ethers

$$ROR' + HI \longrightarrow RI + R'OH$$

Ethers may be cleaved by heating with concentrated HI or HBr.[243] HCl is seldom successful. HBr reacts more slowly than HI, but it is often a superior reagent, since it causes fewer side reactions. Dialkyl ethers and alkyl aryl ethers may be cleaved. In the latter case the alkyl-oxygen bond is the one broken. As in reaction **0-64,** the actual leaving group is not OR'^-, but OHR'. The *Zeisel method* for determination of methoxy groups consists of running this reaction with HI and measuring the amount of methyl iodide formed. Although alkyl aryl ethers always cleave so as to give an alkyl halide and a phenol, there is no general rule for dialkyl ethers. Often cleavage occurs from both sides, and a mixture of two alcohols and two alkyl halides is obtained. However, methyl ethers are usually cleaved so that methyl iodide or bromide is a product. An excess of HI or HBr converts the alcohol product into alkyl halide, so that dialkyl ethers (but not alkyl aryl ethers) are converted to two moles of alkyl halide. This procedure is often carried out so that a mixture of only two products is obtained instead of four. Cyclic ethers (usually tetrahydrofuran derivatives) may be similarly cleaved (see reaction **0-67** for epoxides). Ethers have also been cleaved with Lewis acids, such as BF_3, BCl_3, BBr_3,[244] or $AlCl_3$.[245] In such cases, the departure of the OR is assisted by complex formation with the Lewis acid:

---

[239] Stephens and Tatlow, Ref. 236, p. 52.

[240] Yarovenko and Raksha, *J. Gen. Chem. USSR* **29,** 2125 (1959).

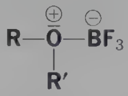
[241] Wiley, Hershkowitz, Rein, and Chung, "Abstracts of Papers," p. 34Q, 145th National Meeting, American Chemical Society, New York, Sept., 1963.

[242] Speziale and Freeman, *J. Am. Chem. Soc.* **82,** 909 (1960).

[243] For a review, see Burwell, *Chem. Rev.* **54,** 615–685 (1954).

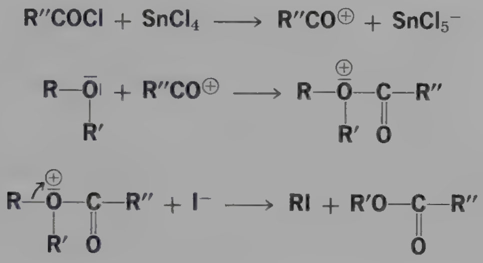
[244] Manson and Musgrave, *J. Chem. Soc.* **1963,** 1011; McOmie and Watts, *Chem. Ind.* (*London*) **1963,** 1658.

[245] For a review, see Johnson, in Olah, "Friedel-Crafts and Related Reactions," vol. 4, pp. 1–109, Interscience Publishers, Inc., New York, 1965.



$$R-\overset{\oplus}{\underset{R'}{O}}-\overset{\ominus}{B}F_3$$

Lewis acids are also used in conjunction with acyl halides. In such cases it is the acyl cation which assists in removal of the leaving group:



$$R''COCl + SnCl_4 \longrightarrow R''CO^{\oplus} + SnCl_5^-$$

$$R-\underset{R'}{\overline{O}}| + R''CO^{\oplus} \longrightarrow R-\overset{\oplus}{\underset{R'}{O}}-\underset{O}{\overset{\|}{C}}-R''$$

$$R-\overset{\oplus}{\underset{R'}{O}}-\underset{O}{\overset{\|}{C}}-R'' + I^- \longrightarrow RI + R'O-\underset{O}{\overset{\|}{C}}-R''$$

Triphenyldibromophosphorane (Ph_3PBr_2) cleaves dialkyl ethers to give two moles of alkyl bromide.[246]

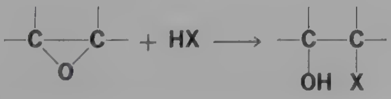
A closely related reaction is cleavage of oxonium salts:

$$R_3O^+ \quad X^- \longrightarrow RX + R_2O$$

For these substrates, HX is not required, and X may be any of the four halide ions.

OS **I**, 150; **II**, 571; **III**, 187, 432, 586, 692, 753, 774, 813; **IV**, 266, 321.

0-66 Formation of halohydrins from epoxides



This is a special case of reaction **0-65** and is frequently used for the preparation of halohydrins.[247] In contrast to the situation with open-chain ethers and with larger rings, epoxides react with all four hydrohalic acids. Chloride and fluoride are strong enough nucleophiles for these substrates because of the strain on the three-membered ring. HI reduces α-keto epoxides to olefins.

OS **I**, 117.

0-67 Conversion of diazo ketones to α-halo ketones

$$RCOCHN_2 + HBr \longrightarrow RCOCH_2Br$$

---

[246] Anderson and Freenor, *J. Am. Chem. Soc.* **86**, 5037 (1964).

[247] For a review, see Winstein and Henderson, in Elderfield, "Heterocyclic Compounds," vol. 1, pp. 23–24, John Wiley & Sons, Inc., New York, 1950.

When diazo ketones are treated with HBr or HCl, they give the respective α-halo ketones. HI does not give the reaction, since it reduces the product to a methyl ketone.

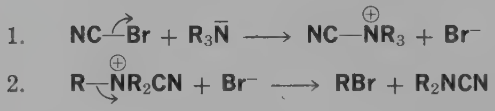
OS **III**, 119.

0-68 Conversion of tertiary amines to N-cyanoamines. The von Braun reaction

$$\mathrm{R_3N + BrCN \longrightarrow R_2NCN + RBr}$$

The *von Braun reaction,* which involves the cleavage of tertiary amines by cyanogen bromide, has been applied to many tertiary amines.[248] Usually, the R group which cleaves is the one which gives the most reactive halide (for example, benzyl or allyl). For simple alkyl groups, the smallest are the most readily cleaved. One or two of the groups on the amine may be aryl, but they do not cleave. Cyclic amines have been frequently cleaved by this reaction. Secondary amines also give the reaction, but the results are usually poor.[249]

The mechanism consists of two successive nucleophilic substitutions, with the tertiary amine as the first nucleophile and the liberated bromide ion as the second:



$$1.\quad \mathrm{NC{-}Br + R_3\bar{N} \longrightarrow NC{-}\overset{\oplus}{N}R_3 + Br^-}$$
$$2.\quad \mathrm{R{-}\overset{\oplus}{N}R_2CN + Br^- \longrightarrow RBr + R_2NCN}$$

OS **III**, 608.

0-69 Cleavage of amines with hydrohalic acids

$$\mathrm{ArNR_2 + HBr \longrightarrow RBr + ArNHR}$$
$$\mathrm{ArNHR + HBr \longrightarrow RBr + ArNH_2}$$

Alkyl groups may be cleaved from secondary and tertiary aromatic amines by concentrated HBr, in a reaction which is similar to reaction **0-65**.[250] Tertiary aliphatic amines are also cleaved by HI, but useful products are seldom obtained.

There are no OS references, but see OS **I**, 428, for a related reaction.

B. Attack at an acyl carbon

0-70 Formation of acyl halides from acids

$$\mathrm{RCOOH + SOCl_2 \longrightarrow RCOCl}$$

---

[248] For a review, see Hageman, *Org. Reactions* **7,** 198–262 (1953).

[249] For a detailed discussion of the scope of the reaction and of the ease of cleavage of different groups, see Ref. 248, pp. 205–225.

[250] Chambers and Pearson, *J. Org. Chem.* **28,** 3144 (1963).

The same inorganic acid halides which convert alcohols to alkyl halides (reaction **0-64**) also convert acids to acyl halides. The reaction is the best and the most common method for the preparation of acyl chlorides. Bromides and iodides are also made in this manner, but much less often. Thionyl chloride is the best reagent, since the byproducts are gases, and the acyl halide is thus easily isolated. Hydrogen halides do not give the reaction. The reaction is unsuccessful for α-keto acids, since under the reaction conditions these compounds give decarbonylation, but if the keto group is protected by conversion to its enol ester, the reaction may be successfully carried out. Acid salts and anhydrides are also sometimes used as substrates. Acyl halides are also used as reagents, in an exchange reaction:

$$\text{RCOOH} + \text{R}'\text{COCl} \rightleftharpoons \text{RCOCl} + \text{R}'\text{COOH}$$

which probably involves an anhydride intermediate. This is an equilibrium reaction, which must be driven to the desired side. Oxalyl chloride and bromide are frequently used as the acyl halide reagent, since oxalic acid decomposes to CO and CO_2, and the equilibrium is thus driven to the side of the other acyl halide.

OS **I,** 12, 147, 394; **II,** 74, 156, 169, 528, 569; **III,** 169, 490, 547, 555, 613, 623, 712, 714; **IV,** 34, 88, 154, 263, 339, 348, 554, 608, 616, 620, 715, 739, 900; **41,** 5, 79.

0-71 Conversion of esters to acyl halides

$$\text{RCOOR}' + \text{PCl}_5 \longrightarrow \text{RCOCl}$$

Acyl halides may be prepared from esters with reagents similar to those used with acids (reaction **0-70**), though esters are much less often used for this purpose. As with reaction **0-70,** acyl halides are sometimes used as reagents, in an exchange reaction. Anhydrides may also serve as substrates.[251]

OS **III,** 422.

0-72 Conversion of hydrazides to acyl halides

$$\text{RCONHNH}_2 + \text{Cl}_2 + \text{HCl} \longrightarrow \text{RCOCl}$$

Treatment of acyl hydrazides with chlorine and HCl gives acyl chlorides. The method is apparently unsuccessful for bromides and iodides.[252]

Hydrogen as Nucleophile. The reactions in this section (**0-73** to **0-80**) are reductions and could have been considered in Chapter 19. They are treated here because they involve replacement of a leaving group by hydrogen, which frequently attacks as the nucleophile hydride ion. However, not all of the reactions in this section are true nucleophilic substitutions, and for some of them, more than one kind of mechanism may be involved, depending on the reagents and on the conditions. When cleavage of a carbon–hetero atom bond is accomplished by catalytic hydrogenation, the reaction is called *hydrogenolysis.*

---

[251] Wale, *Chem. Ind.* (*London*) **1963**, 2003.

[252] Carpino, *J. Am. Chem. Soc.* **79**, 96 (1957).

A. Attack at an alkyl carbon

0-73 Reduction of alkyl halides

$$\mathrm{RX + LiAlH_4 \longrightarrow RH}$$

This type of reduction can be accomplished with many reducing agents, the most common being lithium aluminum hydride.[253] Reduction with lithium aluminum deuteride serves to introduce deuterium into organic compounds. Other reducing agents are zinc (with acid or base), HI, and $SnCl_2$. Sodium arsenite and base, or organotin hydrides R_nSnH_{4-n},[254] can be used to reduce just one halogen of a *gem*-dihalide or a 1,1,1-trihalide. Reduction also may be effected by catalytic hydrogenation. Sodium borohydride does not generally give the reaction, except for very active substrates.

Usually the choice of a reducing agent depends on what other functional groups are present. Each reducing agent reduces certain groups and not others. $LiBH_4$-LiH is *selective* for halogen groups and does not reduce other groups. Most of the reducing agents mentioned reduce chlorides, bromides, and iodides, but organotin hydrides also reduce fluorides. See page 890 for a discussion of selectivity in reduction reactions.

With lithium aluminum hydride and most other metallic hydrides, the mechanism consists of simple nucleophilic substitution with attack by hydride ion, which may or may not be completely free. The mechanism is S_N2 rather than S_N1, since primary halides react better than secondary or tertiary and since Walden inversion has been demonstrated. However, the S_N1 mechanism has been shown for reduction by alkanes (such as isopentane) and aluminum chloride.[255] The aluminum chloride ionizes the substrate, and the resulting carbonium ion abstracts a hydride ion from the alkane:

$$\mathrm{RX + AlCl_3 \longrightarrow \underset{\displaystyle AlCl_3X^-}{\underset{+}{R^+}} + R'H \longrightarrow RH + R'^+}$$

With other reducing agents the mechanism is not always nucleophilic substitution. Some reductions, for example, those with organotin hydrides, take place by free-radical mechanisms[256] and some by electrophilic substitution mechanisms.[257] In the latter case the electrophile is a proton, and the leaving group is X^+.

---

[253] For a discussion of metallic hydrides as reducing agents in this reaction, see Gaylord, "Reduction with Complex Metal Halides," pp. 889–917, Interscience Publishers, Inc., New York, 1956.

[254] Seyferth, Yamazaki, and Alleston, *J. Org. Chem.* **28,** 703 (1963).

[255] Bartlett, Condon, and Schneider, *J. Am. Chem. Soc.* **66,** 1531 (1944); Necşoiu, Bârlădeanu, and Nenitzescu, *Chem. Ind.* (*London*) **1961,** 1753.

[256] Kuivila and Menapace, *J. Org. Chem.* **28,** 2165 (1963); Menapace and Kuivila, *J. Am. Chem. Soc.* **86,** 3047 (1964).

Alkyl halides, including fluorides and polyhalides, may be reduced with magnesium and a secondary or tertiary alcohol (most often isopropyl alcohol).[258] This is actually an example of the occurrence in one step of the sequence:

$$RX \longrightarrow RMgX \xrightarrow{H^+} RH$$

More often, the process is carried out in two separate steps (reaction **2-24,** p. 475, and reaction **2-14,** p. 470).

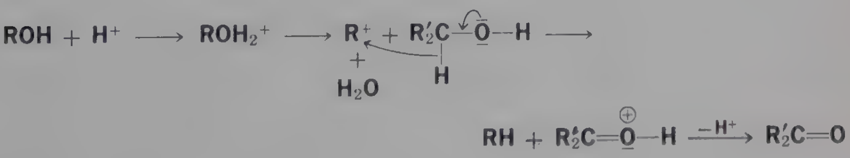
OS **I,** 357, 358, 548; **II,** 320, 393.

0-74 Hydrogenolysis of alcohols

$$ROH + H_2 \xrightarrow{\text{catalyst}} RH$$

The hydroxyl groups of most alcohols can seldom be cleaved by catalytic hydrogenation, and alcohols are often used as solvents for hydrogenation of other compounds. However, benzyl-type alcohols undergo the reaction readily, and these have often been reduced.[259] The most common catalysts are copper chromite and palladium-on-charcoal. Diaryl and triarylcarbonols are similarly easy to reduce, and this has been accomplished with $LiAlH_4$-$AlCl_3$,[260] with alcohols and sulfuric or formic acid,[261] and with iodine and red phosphorus (OS **I,** 224). Other reagents have been used, among them tin and hydrochloric acid. 1,3-Glycols are especially susceptible to hydrogenolysis.

Though the mechanisms of most alcohol reductions are obscure, in at least some cases nucleophilic substitution has been demonstrated. Thus it has been shown by deuterium labeling that, when alcohols are used as reducing agents, it is the α hydrogen which appears at the R group of the newly formed hydrocarbon.[261] In such cases the reducing agent is known to lose a hydride ion.



OS **I,** 224; **IV,** 25, 218, 482; **40,** 16.

[257] For example, see Verkade, de Vries, and Wepster, *Rec. trav. chim.* **83,** 367 (1964).

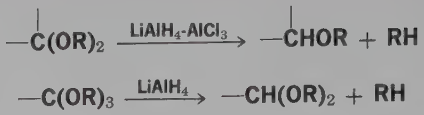
[258] Bryce-Smith, Wakefield, and Blues, *Proc. Chem. Soc.* **1963,** 219.

[259] For a review, see Hartung and Simonoff, *Org. Reactions* **7,** 263–326 (1953).

[260] Blackwell and Hickinbottom, *J. Chem. Soc.* **1961,** 1405.

[261] Dar'eva and Miklukhin, *J. Gen. Chem. USSR* **29,** 620 (1959).

0-75 Replacement of alkoxyl by hydrogen



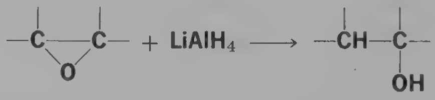
$$-\overset{|}{C}(OR)_2 \xrightarrow{LiAlH_4\text{-}AlCl_3} -\overset{|}{C}HOR + RH$$

$$-C(OR)_3 \xrightarrow{LiAlH_4} -CH(OR)_2 + RH$$

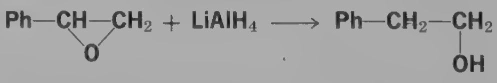
Simple ethers are not normally cleaved by reducing agents, although such cleavage has sometimes been reported (for example, tetrahydrofuran, treated with $LiAlH_4$-$AlCl_3$ gave 1-butanol).[262] Certain types of ethers can be cleaved quite well by reducing agents. Among these are allyl aryl,[263] vinyl aryl,[264] and benzyl ethers (for epoxides, see reaction **0-76**). Acetals and ketals are resistant to $LiAlH_4$ and similar hydrides, and carbonyl groups are often converted to acetals or ketals for protection. However, a combination of $LiAlH_4$ and $AlCl_3$ does reduce acetals and ketals, removing one group, as shown above.[265] Ortho esters are easily reduced to acetals by $LiAlH_4$ alone,[266] offering a route to aldehydes, since these are easily prepared by hydrolysis of the acetals (reaction **0-7**).

OS **III,** 693; **IV,** 798. Also see OS **III,** 742.

0-76 Reduction of epoxides



Reduction of epoxides is a special case of reaction **0-75** and is easily carried out. The mechanism is S_N2, since inversion of configuration has been found. With $LiAlH_4$, cleavage usually occurs so that a tertiary alcohol is formed if that is possible. Next a secondary alcohol is preferred. However, there are exceptions: styrene oxide gives 2-phenylethanol:



The reduction has also been accomplished with other reagents, for example, sodium amalgam in ethanol, and by catalytic hydrogenation.

0-77 Reduction of the C—N bond

$$3RNH_2 + HNF_2 \longrightarrow RH + 2RNH_3^+ \quad F^- + N_2$$

Primary amines have been reduced to alkanes with HNF_2. It is postulated that R—N=N—H is an intermediate,[267] so that the reaction proceeds through the carbonium ion. An indirect means of achieving the same result is conversion of the primary amine to the sulfonamide $RNHSO_2R'$ (reaction **0-101**) and treatment of this with hydroxylamine-O-sulfonic acid ($H_3\overset{\oplus}{N}OSO_3^{\ominus}$).[268] The same intermediate is postulated in this case. Allylic and benzylic amines can be reduced by catalytic hydrogenation.

---

[262] Bailey and Marktscheffel, *J. Org. Chem.* **25,** 1797 (1960).
[263] Tweedie and Cuscurida, *J. Am. Chem. Soc.* **79,** 5463 (1957).
[264] Tweedie and Barron, *J. Org. Chem.* **25,** 2023 (1960).
[265] Eliel, Badding, and Rerick, *J. Am. Chem. Soc.* **84,** 2371 (1962).
[266] Ref. 253, p. 690.
[267] Bumgardner, Martin, and Freeman, *J. Am. Chem. Soc.* **85,** 97 (1963).

Quaternary ammonium salts may be cleaved with $LiAlH_4$[269]

$$R_4N^+ + LiAlH_4 \longrightarrow R_3N + RH$$

as may quaternary phosphonium salts, R_4P^+. Other reducing agents have also been used, for example, sodium in liquid ammonia. When quaternary salts are reduced with sodium amalgam in water, the reaction is known as the *Emde reduction.* However, this reagent is not applicable to the cleavage of ammonium salts with four *saturated* alkyl groups. Some tertiary amines have been cleaved with $LiAlH_4$.[270] Of course, aziridines may be reduced in the same way as epoxides (reaction **0-76**).

OS **III,** 148; **IV,** 508.

For reduction of the C—S bond, see reaction **4-24,** page 556.

B. Attack at an acyl carbon

0-78 Reduction of acyl halides. The Rosenmund reduction

$$RCOCl \xrightarrow[Pd\text{-}BaSO_4]{H_2} RCHO$$

Hydrogenation of acyl halides may be stopped at the aldehyde stage if the catalyst is palladium-on-barium sulfate. This is called the *Rosenmund reduction*[271] and is the most common way of reducing acids to aldehydes, since reduction of acids themselves cannot be stopped at the aldehyde stage (see reaction **9-35,** p. 894). It is sometimes necessary to "poison" the catalyst to prevent further reduction, although many successful reactions have been run without poisons. The most commonly used poison is "quinoline-sulfur," prepared by reflux of sulfur in quinoline. Careful control of the temperature may achieve the same effect. The reduction has also been carried out with $LiAlH(O\text{-}tert\text{-}Bu)_3$,[272] with Bu_3SnH,[273] and by irradiation in the presence of a hydrogen donor.[274] In the two latter cases, the mechanisms are free-radical. There are several indirect methods for the conversion of acyl halides to aldehydes, most of them involving prior conversion of the halides to certain types of amides (see reaction **0-80**).[275] Also see reaction **9-41,** page 897.

OS **III,** 551, 627. Also see OS **III,** 818.

---

[268] Nickon and Hill, *J. Am. Chem. Soc.* **86,** 1152 (1964).

[269] For a review, see Ref. 253, pp. 781–793.

[270] Tweedie and Allabash, *J. Org. Chem.* **26,** 3676 (1961).

[271] For a review, see Mosettig and Mozingo, *Org. Reactions* **4,** 362–377 (1948).

[272] Brown and McFarlin, *J. Am. Chem. Soc.* **80,** 5372 (1958).

[273] Kuivila, *J. Org. Chem.* **25,** 284 (1960); Kuivila and Walsh, *J. Am. Chem. Soc.* **88,** 571 (1966).

[274] Schmidt, *Angew. Chem. Intern. Ed. Engl.* **4,** 146 (1965).

[275] For a review, see Mosettig, *Org. Reactions* **8,** 218–257 (1954).

0-79 Reduction of acids and esters to aldehydes

$$\mathrm{RCOOH} \not\longrightarrow \mathrm{RCHO}$$

Reduction of acids to aldehydes is generally not feasible, since reducing agents normally give alcohols (reaction **9-35**, p. 894). However, lithium in ethylamine gives good yields of high-molecular-weight fatty aldehydes, such as stearaldehyde,[276] and some aldehydes have been prepared by heating carboxylic acids with formic acid and thorium oxide (this is actually an example of reaction **0-98**). Caproic and isovaleric acids have been reduced to aldehydes, in 50% yields or better, with (*iso*-Bu)$_2$AlH at $-75°$ to $-70°$.[277]

Esters have been reduced to aldehydes with (*iso*-Bu)$_2$AlH at $-70°$, with NaAlH$_4$ at $-65°$ to $-45°$, and (for phenolic esters) with Li(*tert*-Bu)$_3$AlH at 0°.[278] Also see reactions **9-37** and **9-39**, page 896.

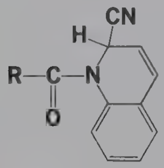
0-80 Reduction of amides to aldehydes

$$\mathrm{RCONR'_2} + \mathrm{LiAlH_4} \longrightarrow \mathrm{RCHO} + \mathrm{NHR'_2}$$

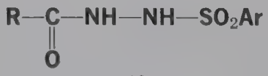
N,N-Disubstituted amides can be reduced to amines (see reaction **9-36**, p. 895), but also to aldehydes.[279] Keeping the amide in excess gives the aldehyde rather than the amine. Sometimes it is not possible to prevent further reduction, and primary alcohols are obtained instead. Other reagents which give good yields of aldehydes are (*iso*-Bu)$_2$AlH,[280] (*tert*-BuO)$_3$LiAlH, and LiAlH$_4$-EtOH.[281]

Aldehydes have been prepared from acids or acyl halides by first converting them to certain types of amides which are easily reducible. The following are some examples:

1. *Reissert compounds*[275] (**51**) are prepared from the acyl halide by treatment with quinoline and cyanides. Treatment of **51** with sulfuric acid gives the corresponding aldehyde.

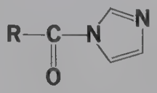


51

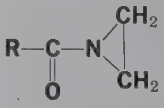


$$\mathrm{R{-}\underset{\|}{\overset{}{C}}{-}NH{-}NH{-}SO_2Ar}\quad(\mathrm{C{=}O})$$

52



53



54

---

[276] Burgstahler, Worden, and Lewis, *J. Org. Chem.* **28,** 2918 (1963).

[277] Zakharkin and Khorlina, *J. Gen. Chem. USSR* **34,** 1021 (1964).

[278] Zakharkin and Khorlina, *Tetrahedron Letters* **1962,** 619, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963,** 288–290, **1964,** 435; Zakharkin, Gavrilenko, Maslin, and Khorlina, *Tetrahedron Letters* **1963,** 2087; Zakharkin, Gavrilenko, and Maslin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964,** 867; Weissman and Brown, *J. Org. Chem.* **31,** 283 (1966).

[279] For a review, see Ref. 253, pp. 575–590.

[280] Zakharkin and Khorlina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1959,** 2046.

[281] Brown and Tsukamoto, *J. Am. Chem. Soc.* **86,** 1089 (1964).

2. Acylsulfonylhydrazides (**52**) are cleaved with base to give aldehydes. This is known as the *McFadyen-Stevens reduction*[275] and is applicable only to aromatic aldehydes, or to aliphatic aldehydes with no α hydrogen.[282] RCON=NH (see reaction **0-77**) has been proposed as an intermediate in this reaction.

3. Imidazoles (**53**)[283] and N-acylaziridines (**54**)[284] may be reduced to aldehydes with $LiAlH_4$.

See OS **IV,** 641, for the preparation of a Reissert compound.

Carbon Nucleophiles. In any ionic reaction in which a new carbon-carbon bond is formed, one carbon atom is attacking as a nucleophile and the other as an electrophile. Whether to classify a given reaction as nucleophilic or electrophilic is a matter of convention and is usually based on analogy. Although not discussed in this chapter, reactions **1-12** to **1-28** and **2-9** to **2-11** are actually nucleophilic substitutions with respect to one reactant, although, following convention, we classify them with respect to the other. Similarly, all the reactions in this section (**0-81** to **0-98**) would be called electrophilic substitutions (aromatic or aliphatic) if we were to consider the reagent as the substrate.

A. Attack at an alkyl carbon. In reactions **0-81** to **0-84** the nucleophile is the "carbanion" part of an organometallic compound, most often a Grignard reagent. Whether or not free carbanions are actually involved, the attacking carbon brings a pair of electrons with it to the new C—C bond.

0-81 Coupling of organometallics with alkyl halides. The Wurtz reaction

$$RX + R'M \longrightarrow RR'$$

The connection of two alkyl groups is called *coupling*. It may often be accomplished by the treatment of an alkyl halide with an organometallic compound, though the scope is limited by the low reactivity of some organometallics and the high reactivity, resulting in side reactions, of others. When the organometallic compound is a Grignard reagent,[285] coupling takes place readily with active halides: allylic (though allylic rearrangements are common) and benzylic, e.g.,

$$PhCH_2Cl + CH_3CH_2MgCl \longrightarrow PhCH_2CH_2CH_3$$

Tertiary alkyl halides also couple with Grignard reagents, but in low yields (30 to 50%). Aryl Grignard reagents also couple with these substrates and indeed usually give better yields. Although the coupling of Grignard reagents with ordinary alkyl halides is usually not useful for synthetic purposes, small amounts of symmetrical coupling product are commonly formed while Grignard reagents are being prepared. The usual method for the preparation of Grignard reagents consists of the addition of the halide to magnesium in ether. The coupling products arise from reaction of some of the RMgX which is initially formed with fresh RX which is being added to the solution. Alkylzinc compounds are sometimes used instead of Grignard reagents and behave similarly.

---

[282] Sprecher, Feldkimel, and Wilchek, *J. Org. Chem.* **26**, 3664 (1961); Babad, Herbert, and Stiles, *Tetrahedron Letters* **1966**, 2927.

[283] For a review, see Staab, *Angew. Chem. Intern. Ed. Engl.* **1**, 351–367 (1962), pp. 360–361.

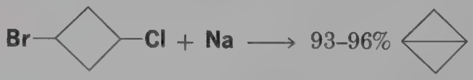
[284] Brown and Tsukamoto, *J. Am. Chem. Soc.* **83**, 4549 (1961).

[285] For a review, see Kharasch and Reinmuth, "Grignard Reactions of Nonmetallic Substances," pp. 1046–1165, Prentice-Hall, Inc., Englewood Cliffs, N.J., 1954.

Organosodium and -potassium compounds are more reactive than Grignard reagents and should couple even with less reactive halides. The difficulty is in preparing and keeping them long enough for the alkyl halide to be added. With particularly stable organosodium or -potassium reagents, such as triphenylmethylsodium, coupling can be accomplished even with primary and secondary halides.

When sodium metal is added to an alkyl halide, the RNa first formed immediately attacks another RX, so that a symmetrical alkane RR is produced. This is called the *Wurtz reaction.* Side reactions (elimination and rearrangement) are so common that the reaction is seldom used. When a mixture of an alkyl halide and an aryl halide is treated with sodium, the sodium preferentially attacks the aryl halide to form arylsodium, which then attacks the alkyl halide to give an alkylated aromatic compound. This mixed Wurtz reaction is called the *Wurtz-Fittig reaction.* Mixed Wurtz reactions of two alkyl halides are not feasible because of the number of products obtained. The coupling of two aryl groups by this method is also not feasible, owing to the low reactivity of aryl halides toward nucleophilic substitution (however, see reaction **3-16**, p. 507). Other metals have also been used to effect Wurtz reactions, notably silver and zinc.[286] Halides containing aryl groups (e.g., benzyl chloride) may be coupled with Grignard reagents if a small amount of a catalyst such as $CoCl_2$ or $FeCl_3$ is present.[287] The Grignard reagent is not found in the product here. For example, benzyl chloride gives bibenzyl regardless of which Grignard reagent is used.

The Wurtz reaction may be used for ring closure, especially for three-membered rings. For example, 1,3-dibromopropane may be converted to cyclopropane by zinc and sodium iodide. An interesting use of this reaction is in the preparation of bicyclobutane.[288]



There has been much speculation about the mechanism of the Wurtz and closely related reactions. It seems agreed that it is usually nucleophilic substitution.[289] The finding, in the case of optically active 1-phenylethyl chloride or bromide treated with sodium, lithium, or potassium in liquid ammonia, that the 2,3-diphenylbutane produced was optically active,[290] is evidence that, at least in this case, the mechanism is S_N2, since free radicals do not retain or invert configuration. However, free-radical mechanisms have been demonstrated in some cases.[291]

---

[286] See, for example, Nosek, *Collection Czech. Chem. Commun.* **29,** 597 (1964).

[287] Sayles and Kharasch, *J. Org. Chem.* **26,** 4210 (1961).

[288] Wiberg and Lampman, *Tetrahedron Letters* **1963,** 2173.

[289] LeGoff, Ulrich, and Denney, *J. Am. Chem. Soc.* **80,** 622 (1958).

[290] Verkade, de Vries, and Wepster, *Rec. trav. chim.* **83,** 1149 (1965).

OS **I,** 186; **III,** 121, 157; **IV,** 748; **44,** 30; **46,** 115. Also see OS **IV,** 877, 914.

0-82 Coupling of Grignard reagents with esters of sulfuric and sulfonic acids

$$\mathrm{ROSO_2OR' + R''MgX \longrightarrow RR''}$$

Coupling with alkyl sulfates and sulfonates is most often carried out with Grignard reagents prepared from aryl halides.[292] Alkyl sulfates and sulfonates generally make more successful substrates in this reaction than the corresponding alkyl halides (reaction **0-81**). The method is useful for primary and secondary R.

OS **I,** 471; **II,** 47, 360.

0-83 Coupling of Grignard reagents with ethers

$$\mathrm{ROAr + R''MgX \longrightarrow RR'' + ArOMgX}$$

$$\mathrm{R_2C(OR')_2 + R''MgX \longrightarrow R_2CR''(OR') + R'OMgX}$$

$$\mathrm{RC(OR')_3 + R''MgX \longrightarrow RCR''(OR')_2 + R'OMgX}$$

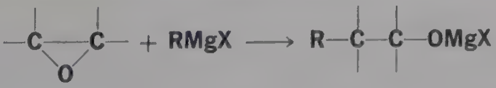
Ordinary ethers are not cleaved by Grignard reagents, though more active organometallic compounds often do cleave them.[293] Phenolic ethers have been cleaved, as shown above, by heating to a high temperature with Grignard reagents. Acetals, ketals, and ortho esters react quite well with Grignard reagents to give, respectively, ethers and acetals (or ketals). The latter may be hydrolyzed to aldehydes or ketones (reaction **0-7**). Tertiary amines may be prepared by the reaction of amino ethers with Grignard reagents:

$$\mathrm{R_2N{-}CH_2{-}OR' + R''MgX \longrightarrow R_2N{-}CH_2{-}R''}$$

Also see reaction **0-84.**

OS **II,** 323; **III,** 701.

0-84 The reaction of Grignard reagents with epoxides



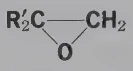
---

[291] Bryce-Smith, *Bull. Soc. chim. France* **1963,** 1418; D'yachkovskii and Shilov, *J. Gen. Chem. USSR* **33,** 400 (1963).

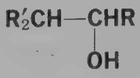
[292] For a review, see Ref. 285, pp. 1277–1286.

[293] For a review of the reactions of ethers with Grignard reagents, see Ref. 285, pp. 1013–1045.

The reaction between Grignard reagents and epoxides is very valuable and is often used to increase the length of a carbon chain by two carbons.[294] The Grignard reagent may be aromatic or aliphatic, though tertiary Grignard reagents give low yields. When *gem*-disubstituted epoxides (**55**) are used (and sometimes otherwise), the product may be **56**; that is, the new alkyl



55



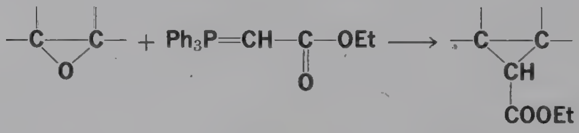
$R'_2CH-\underset{OH}{C}HR$

56

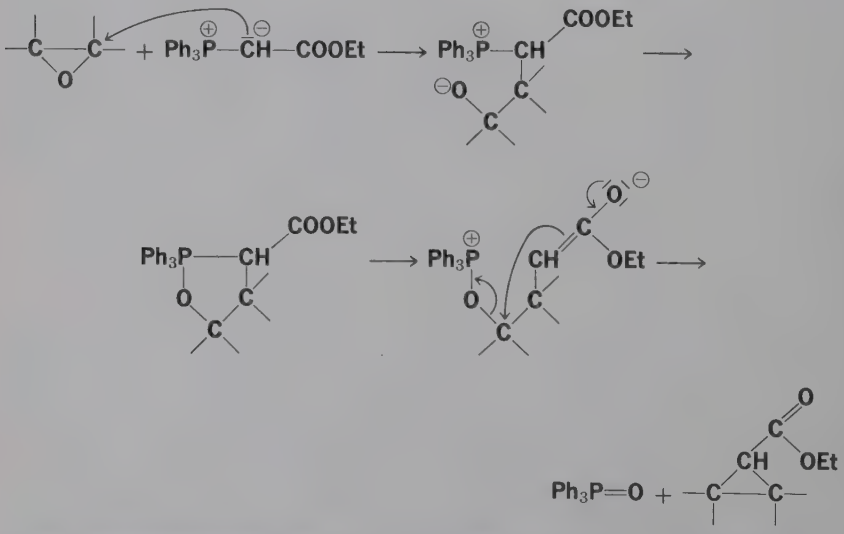
group may appear on the same carbon as the OH. In such cases, the epoxide is isomerized to an aldehyde or a ketone before reacting with the Grignard reagent. Halohydrins are often side products.

OS **I**, 306.

0-85 The conversion of epoxides to cyclopropanes



The treatment of epoxides with certain phosphorus ylides gives substituted cyclopropanes[295] in a reaction which is mechanistically related to reaction **0-84**. In this reaction the initial attack on the epoxide is similar to that of the Grignard reagent:



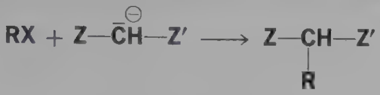
---

[294] For reviews, see Gaylord and Becker, *Chem. Rev.* **49**, 413–533 (1951); and Ref. 285, pp. 961–1012.

[295] Denney, Vill, and Boskin, *J. Am. Chem. Soc.* **84**, 3944 (1962). Also see Trippett, *Quart. Rev. (London)* **17**, 406–440 (1964), pp. 426–428.

The final step is also a nucleophilic substitution, with $OPPh_3$ as the leaving group. Nucleophilic attack by phosphorus ylides is also found in reaction **0-95** and in the Wittig reaction (**6-45,** p. 702).

0-86 Alkylation at a carbon bearing an active hydrogen

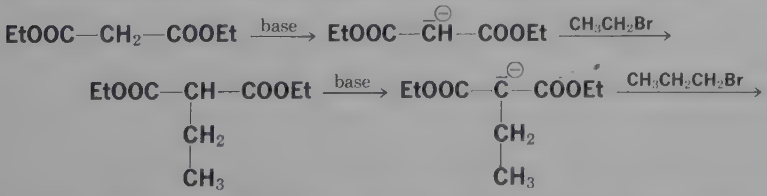


$$RX + Z-\overset{\ominus}{\bar{C}}H-Z' \longrightarrow Z-\underset{R}{\underset{|}{C}}H-Z'$$

Compounds which contain two (or three, but this is rare) strong electron-withdrawing groups on a carbon atom are more acidic than compounds without such groups and are easily converted to carbanions. These carbanions can attack alkyl halides, resulting in their alkylation.[296] Z and Z′ may be $COOR'$, CHO, COR', $CONR'_2$, COO^-, CN, NO_2, SO_2R', SO_2OR', $SO_2NR'_2$, or similar groups. A carbon atom with any two of these, the same or different, will give up a proton (if it has one) to a base such as sodium, sodium ethoxide, or in some cases sodium hydroxide. Usually the reaction is carried out on a CH_2 group connected to two Z groups. In such cases it is possible to alkylate twice, first removing the proton with a base, then alkylating with RX, then removing the remaining proton from ZCHRZ′, and finally alkylating the resulting carbanion with the same or a different alkyl halide. The reactions fail with tertiary RX, since these undergo elimination under the reaction conditions.

The reaction is occasionally performed on compounds with only one Z group if the group is a particularly strong electron-withdrawing group, such as nitro, or if a particularly strong base, such as sodium amide, potassium *tert*-butoxide, or sodium triphenylmethyl is used. However, in the latter type of case, yields are often low. Aside from nitro compounds, which perform quite well, the compounds containing only one Z are most often ketones, esters, and nitriles.[297] Z may also be phenyl, but when two phenyl groups are on the same carbon, the acidity is less than in the other cases. Nevertheless, the reaction has been successfully carried out with diphenylmethane, with sodium amide as the base.[298] In many cases there is a possibility of competing O-alkylation (see ambident nucleophiles, p. 298).

An important example of this reaction is the *malonic ester synthesis,* in which both Z groups are COOEt. The product may be hydrolyzed and decarboxylated (reaction **2-26,** p. 477) to give a carboxylic acid. An illustration is the preparation of 2-ethylpentanoic acid from malonic ester:



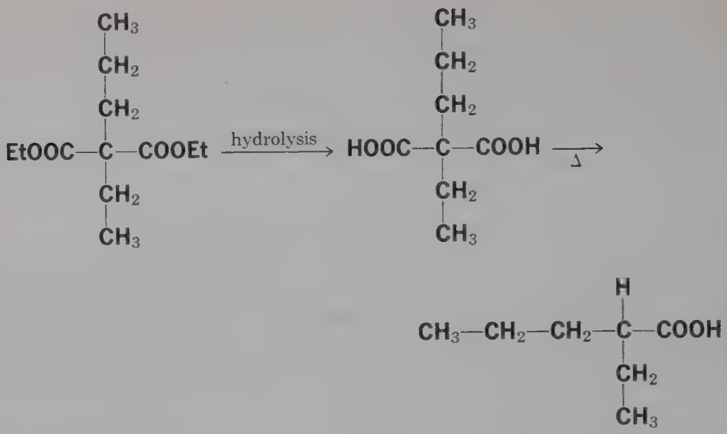
$$EtOOC-CH_2-COOEt \xrightarrow{\text{base}} EtOOC-\overset{\ominus}{\bar{C}}H-COOEt \xrightarrow{CH_3CH_2Br}$$
$$EtOOC-\underset{\underset{CH_3}{CH_2}}{CH}-COOEt \xrightarrow{\text{base}} EtOOC-\underset{\underset{CH_3}{CH_2}}{\overset{\ominus}{\bar{C}}}-COOEt \xrightarrow{CH_3CH_2CH_2Br}$$

---

[296] For a review, see House, "Modern Synthetic Reactions," pp. 163–204, Benjamin, New York, 1965.

[297] For a review of alkylation of esters and nitriles, see Cope, Holmes, and House, *Org. Reactions* **9,** 107–331 (1957).

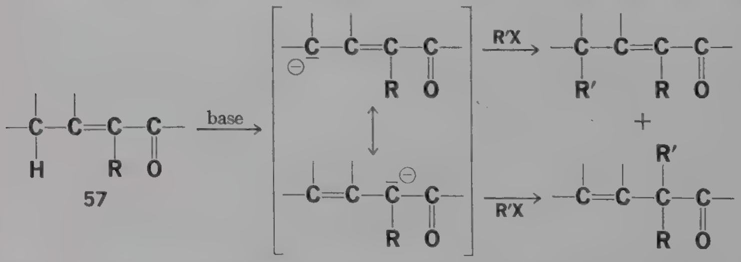
[298] See, for example, Hauser and Hamrick, *J. Am. Chem. Soc.* **79,** 3142 (1957); Hauser, Hauser, and Hamrick, *J. Org. Chem.* **24,** 397 (1959).



Other important examples are the *acetoacetic ester synthesis,* in which Z is COOEt and Z′ is $COCH_3$, and the product may be decarboxylated to a ketone, and the *cyanoacetic ester synthesis,* in which Z is COOEt and Z′ is CN. In this case too, the product may be hydrolyzed and decarboxylated. When the reaction is applied to N-acetylaminomalonic ester [$(EtOOC)_2CHNHCOCH_3$], the product may be hydrolyzed and decarboxylated to give α-amino acids. This is known as the *Sorensen method* of amino acid synthesis.

The reaction is not limited to $Z—CH_2—Z'$ and $Z—CH_3$ compounds. Other acidic C—H hydrogens, which include, for example, the methyl hydrogens of α-methylpyridines, hydrogens α to an arylalkylamino nitrogen (that is $\underline{H}CH_2NPhMe$),[299] the CH_2 hydrogens of cyclopentadiene and its derivatives, hydrogens on a triple-bond carbon (see reaction **0-87**), and the hydrogen of HCN (see reaction **0-88**), may also be removed with a base and the resulting ion alkylated.

In compounds containing the system **57**, the γ hydrogen assumes the acidity normally held by the position α to the carbonyl group, especially when R is not hydrogen and so cannot compete. This principle, called *vinylology,* operates because the resonance effect is transmitted through the double bond. However, because of the resonance, alkylation at the α position (with allylic rearrangement) competes with alkylation at the γ position, and often predominates.



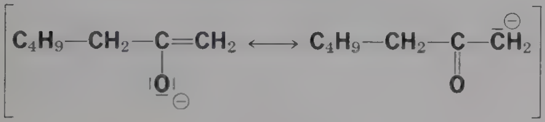
57

---

[299] Lepley and Giumanini, *Chem. Ind.* (*London*) **1965,** 1035.

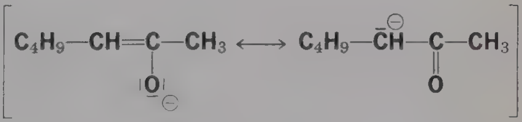
Alkylation always takes place at the most acidic position of a reagent molecule; for example, acetoacetic ester (CH_3COCH_2COOEt) is alkylated at the methylene and not at the methyl group, because the former is more acidic than the latter and hence gives up its proton to the base. However, if two moles of base are used, then not only is the most acidic proton removed but also the second most acidic. Alkylation of this doubly charged anion then takes place at the less-acidic position (see p. 299). This technique has been used to alkylate many compounds in the second most acidic position.[123]

When the reaction is carried out with nonsymmetrical ketones containing no other functional groups, alkylation is sometimes found on the more highly substituted carbon, and sometimes on the less highly substituted one. The direction of attack depends on the nature of the substrate and on the solvent.[300] In any case, di- and trisubstitution are frequent, and it is often difficult to stop with the introduction of just one alkyl group. One method of alkylating the *desired* side of an unsymmetrical ketone involves prior preparation of the desired one of the two possible enolates. The two enolates, e.g., **58** and **59** for 2-heptanone,



$$\left[C_4H_9-CH_2-\underset{|\underline{O}|^{\ominus}}{\underset{|}{C}}=CH_2 \longleftrightarrow C_4H_9-CH_2-\underset{O}{\underset{\|}{C}}-\overset{\ominus}{\bar{C}}H_2 \right]$$

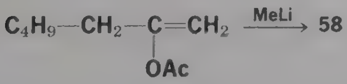
58



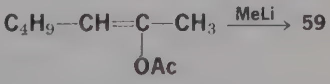
$$\left[C_4H_9-CH=\underset{|\underline{O}|^{\ominus}}{\underset{|}{C}}-CH_3 \longleftrightarrow C_4H_9-\overset{\ominus}{\bar{C}}H-\underset{O}{\underset{\|}{C}}-CH_3 \right]$$

59

interconvert rapidly only in the presence of the parent ketone or of any stronger acid.[301] In the absence of such acids, it is possible to prepare either **58** or **59** and thus achieve selective alkylation on either the more or less highly alkylated side of the ketone.[302] The desired enolate may be obtained by treatment of the corresponding enol acetate with two equivalents of methyllithium in 1,2-dimethoxyethane. Each enol acetate gives the corresponding enolate, e.g.,



$$C_4H_9-CH_2-\underset{OAc}{\underset{|}{C}}=CH_2 \xrightarrow{MeLi} \mathbf{58}$$



$$C_4H_9-CH=\underset{OAc}{\underset{|}{C}}-CH_3 \xrightarrow{MeLi} \mathbf{59}$$

The enol acetates, in turn, may be prepared by treatment of the parent ketone with an appropriate reagent.[302] Such treatment generally gives a mixture of the two enol acetates in which one or the other predominates, depending on the reagent. The mixtures are easily separable.[302]

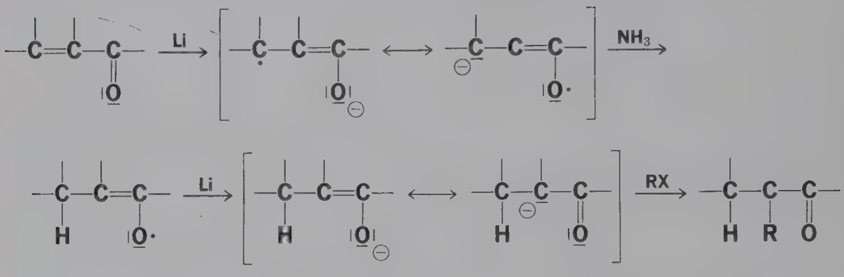
Another method of assuring that alkylation of a ketone takes place on the desired side of the carbonyl group involves the treatment of an α,β-unsaturated ketone with lithium in liquid ammonia prior to the addition of the alkyl halide.[303] The lithium and ammonia reduce the ketone to an enolate ion, which attacks the alkyl halide (see the Birch reduction, **5-12**, p. 597):

---

[300] House, Ref. 296.

[301] House and Trost, *J. Org. Chem.* **30,** 1341 (1965).

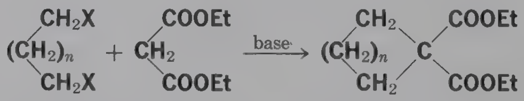
[302] House and Trost, *J. Org. Chem.* **30,** 2502 (1965).



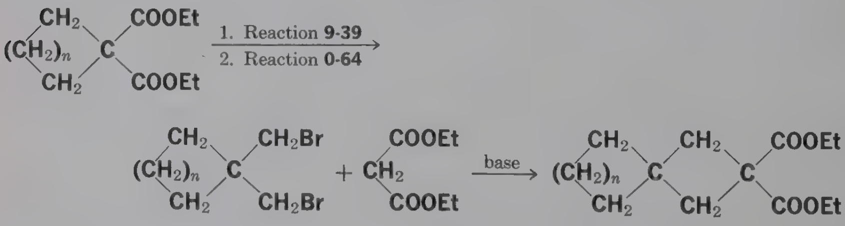
Alkylation must therefore take place on the side of the double bond. Of course, this method is not actually an alkylation of the ketone, but of the α,β-unsaturated ketone, though the product is the same as if the saturated ketone had been alkylated on the desired side.

Another method for the alkylation of ketones is the Stork enamine reaction (**2-10**, p. 464).

When ω,ω'-dihalides are used, ring closures may be effected:



The method has been used to close rings of from three ($n = 0$) to seven members, although five-membered-ring closures proceed in highest yields. When malonic ester is used for ring closure, it is possible to convert the carbethoxyl groups to CH_2Br groups, and repeat the process with another mole of malonic ester. This gives rise to spiranes, e.g.,



The process may be repeated, and di-, tri-, and tetraspiranes have been made in this manner.[304]

Other leaving groups are sometimes used. Sulfates, sulfonates, and epoxides give the expected products. Acidified hydroxy[305] (from triphenylcarbinol) and NR_2 (in Mannich bases such as $RCOCH_2CH_2NR_2$)[306] groups have also been used as leaving groups.

---

[303] Stork, Rosen, Goldman, Coombs, and Tsuji, *J. Am. Chem. Soc.* **87**, 275 (1965).

[304] Buchta and Geibel, *Ann.* **648**, 36 (1961), **678**, 53 (1964); Buchta and Theuer, *Ann.* **666**, 81 (1963); Buchta and Billenstein, *Ann.* **685**, 74 (1965); Buchta and Merk, *Ann.* **694**, 1 (1966).

OS **I,** 248, 250; **II,** 262, 279, 384, 474; **III,** 44, 213, 219, 221, 223, 397, 405, 495, 705; **IV,** 10, 55, 278, 288, 291, 597, 623, 641, 962; **40,** 38; **41,** 56, 99; **42,** 75.

0-87 Alkylation at an acetylenic carbon

$$RX + R'C{\equiv}C^- \longrightarrow RC{\equiv}CR'$$

The reaction between alkyl halides and acetylide ions is quite useful, but is of limited scope.[307] Only unbranched primary halides give good yields. If acetylene is the reagent, two different groups may be successively attached. Sulfates and sulfonates are sometimes used as substrates. A convenient method for preparation of the acetylide ion is the addition of the alkyne to a solution of $CH_3SOCH_2^-$ in dimethyl sulfoxide.[308] This solution may be prepared by the addition of sodium hydride to dimethyl sulfoxide.

OS **IV,** 117. Also see OS **IV,** 801.

0-88 Preparation of nitriles

$$RX + CN^- \longrightarrow RCN$$

The reaction between cyanide ion and alkyl halides represents a convenient method for the preparation of nitriles.[309] Primary halides give good yields of nitriles; secondary halides give low yields. The reaction fails for tertiary halides, which give elimination under these conditions. Many other groups on the molecule do not interfere. This is an important way of increasing the length of a carbon chain by one carbon, since nitriles are easily hydrolyzed to carboxylic acids (reaction **6-5,** p. 660). The cyanide ion is an ambident nucleophile, and isonitriles may be side products, and sometimes the main products, especially if the reagent is silver cyanide. The cyanide nucleophile also reacts with compounds containing other leaving groups. Esters of sulfuric and sulfonic acids behave like halides. Epoxides give β-hydroxy nitriles. Ortho esters give α-cyano acetals:

$$RC(OR')_3 + HCN \xrightarrow{ZnCl_2} NC{-}CR(OR')_2$$

With certain β-dialkylaminoethyl aryl ketones, NMe_2 may be the leaving group (elimination-addition mechanism):

$$ArCOCH_2CH_2NMe_2 + CN^- \longrightarrow ArCOCH_2CH_2CN$$

---

[305] Patai and Dayagi, *J. Chem. Soc.* **1962,** 716.

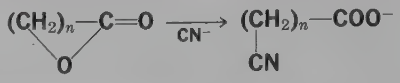
[306] For a review, see Brewster and Eliel, *Org. Reactions* **7,** 99–197 (1953).

[307] For a review, see Jacobs, *Org. Reactions* **5,** 25–40 (1949).

[308] Kříž, Beneš, and Peška, *Tetrahedron Letters* **1965,** 2881.

[309] For a review, see Mowry, *Chem. Rev.* **42,** 189–283 (1948), pp. 191–206, 244–246.

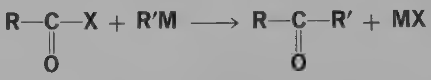
Lactones may be opened up with potassium cyanide:



OS **I,** 46, 107, 156, 181, 254, 256, 536; **II,** 292, 376; **III,** 174, 372, 557; **IV,** 438, 496, 576; **40,** 45; **46,** 48.

B. Attack at an acyl carbon[310]

0-89 The conversion of acyl halides to ketones with organometallic compounds[311]

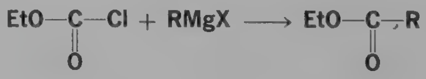


$$R{-}\underset{\underset{O}{\|}}{C}{-}X + R'M \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}R' + MX$$

When acyl halides are treated with Grignard reagents, the products are usually tertiary alcohols (see reaction **6-33,** p. 688) because the ketones initially formed further react with the Grignard reagent. Ketones *have* been prepared in this manner, by the use of low temperatures, inverse addition (i.e., addition of the acyl halide to the Grignard reagent, rather than the other way around), excess acyl halide, etc., but the yields are usually low. Some ketones are unreactive toward Grignard reagents for steric or other reasons, and these may be prepared in this way. Also, certain metallic halides, notably ferric chloride, are catalysts which improve the yields of ketone at the expense of tertiary alcohol.[312] For these catalysts, a free-radical mechanism has been proposed.

In contrast to Grignard reagents, organocadmium compounds (prepared from Grignard reagents, see reaction **2-21,** p. 474) react with acyl halides to give good yields of ketones, in a reaction of wide scope. Both R and/or R′ may be aryl. Since organocadmium compounds do not react with esters, these groups may be present in either molecule. Organozinc compounds behave similarly but are less often used.

Grignard reagents react with ethyl chloroformate to give esters.



$$EtO{-}\underset{\underset{O}{\|}}{C}{-}Cl + RMgX \longrightarrow EtO{-}\underset{\underset{O}{\|}}{C}{-}R$$

OS **II,** 198; **III,** 601; **IV,** 708.

0-90 The conversion of anhydrides, esters, or amides to ketones with organometallic compounds[313]

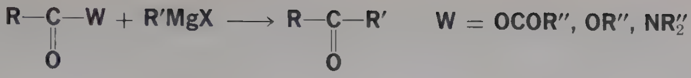
---

[310] For a discussion of many of the reactions in this section, see House, "Synthetic Organic Reactions," pp. 257–281, Benjamin, New York, 1965.

[311] For reviews, see Ref. 285, pp. 712–724; Shirley, *Org. Reactions* **8,** 28–58 (1954).

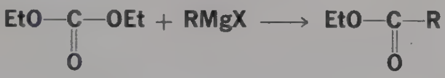
[312] Cason and Kraus, *J. Org. Chem.* **26,** 1768, 1772 (1961).

[313] For a review, see Ref. 285, pp. 561–562, 846–908.



$$R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}W + R'MgX \longrightarrow R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R' \qquad W = OCOR'', OR'', NR''_2$$

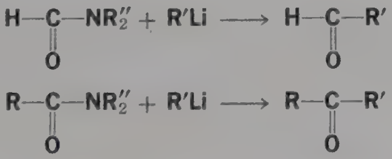
As is the case with acyl halides (reaction **0-89**), anhydrides and esters also give tertiary alcohols (reaction **6-33**, p. 688) when treated with Grignard reagents. Low temperatures[314] and inverse addition have been used to increase the yields of ketone. Amides give better yields of ketone at room temperature, but still only about 10 to 50%. Organocadmium reagents are less successful with these substrates than with acyl halides (reaction **0-89**). Esters of formic acid, and dialkylformamides, give good yields of aldehydes, since these are less reactive toward Grignard reagents. Ethyl carbonate has been used to prepare esters



$$EtO{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OEt + RMgX \longrightarrow EtO{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R$$

but more often the reaction goes further to give the ketone or the tertiary alcohol.

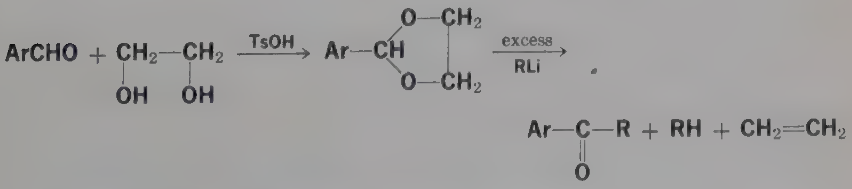
Alkyllithium compounds have been used to give good yields of ketones from esters. The reaction must be carried out in a high-boiling solvent such as toluene, since reaction at lower temperatures gives tertiary alcohols.[315] Alkyllithiums also give good yields of carbonyl compounds with N,N-disubstituted amides.[316] Dialkylformamides give aldehydes, and other tertiary amides give ketones.



$$H{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}NR''_2 + R'Li \longrightarrow H{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R'$$

$$R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}NR''_2 + R'Li \longrightarrow R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R'$$

Alkyl aryl ketones may be prepared in good yields from aromatic aldehydes. The aldehydes are converted to the corresponding cyclic acetals, and these are treated with excess alkyllithium reagent.[317]



---

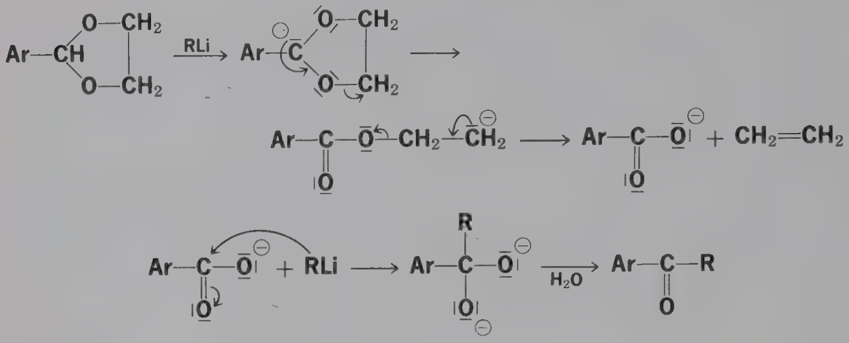
[314] See, for example, Newman and Booth, *J. Am. Chem. Soc.* **67**, 154 (1945); Newman and Smith, *J. Org. Chem.* **13**, 592 (1948); Edwards and Kammann, *J. Org. Chem.* **29**, 913 (1964).

[315] Petrov, Kaplan, and Tsir, *J. Gen. Chem. USSR* **32**, 691 (1962).

[316] Evans, *J. Chem. Soc.* **1956**, 4691; Izzo and Safir, *J. Org. Chem.* **24**, 701 (1959).

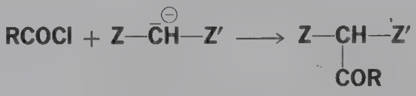
[317] Berlin, Rathore, and Peterson, *J. Org. Chem.* **30**, 226 (1965).

The reaction is mentioned in this section because the product-determining step is a reaction between $ArCOO^-$ and RLi:



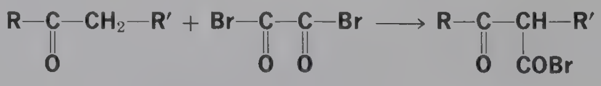
OS **II**, 282; **III**, 353; **IV**, 285.

0-91 Acylation by acyl halides, at a carbon bearing an active hydrogen



$$RCOCl + Z{-}\overset{\ominus}{C}H{-}Z' \longrightarrow Z{-}\underset{COR}{\underset{|}{CH}}{-}Z'$$

This reaction is similar to reaction **0-86**, though many fewer examples have been reported. Z and Z′ may be any of the groups listed at **0-86**. As in that case, two such groups are usually necessary, unless a very strong base is used to create the anion. For example, esters RCH_2COOEt may be acylated at the α-carbon if sodium triphenylmethyl is used to remove the proton. When two Z groups are present, then the product contains three Z groups on one carbon, since RCO is a Z group. One or two of these may then be cleaved (reaction **2-29**, p. 481). In this way a compound $Z{-}CH_2{-}Z'$ may be converted to $Z{-}CH_2{-}Z''$. Ketones have been acylated by oxalyl bromide, with CO being lost in the process:[318]

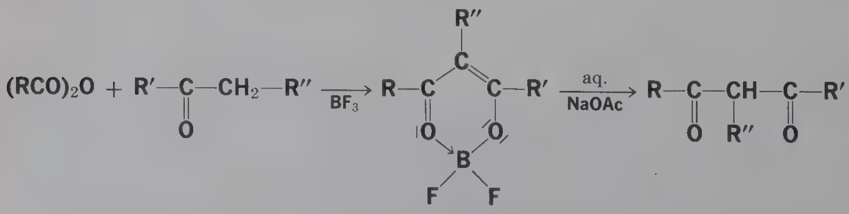


$$R{-}\underset{O}{\underset{\|}{C}}{-}CH_2{-}R' + Br{-}\underset{O}{\underset{\|}{C}}{-}\underset{O}{\underset{\|}{C}}{-}Br \longrightarrow R{-}\underset{O}{\underset{\|}{C}}{-}\underset{COBr}{\underset{|}{CH}}{-}R'$$

O-Acylation is sometimes a side reaction.

OS **II**, 266, 268, 594, 596; **III**, 390, 637; **IV**, 415; **42**, 41.

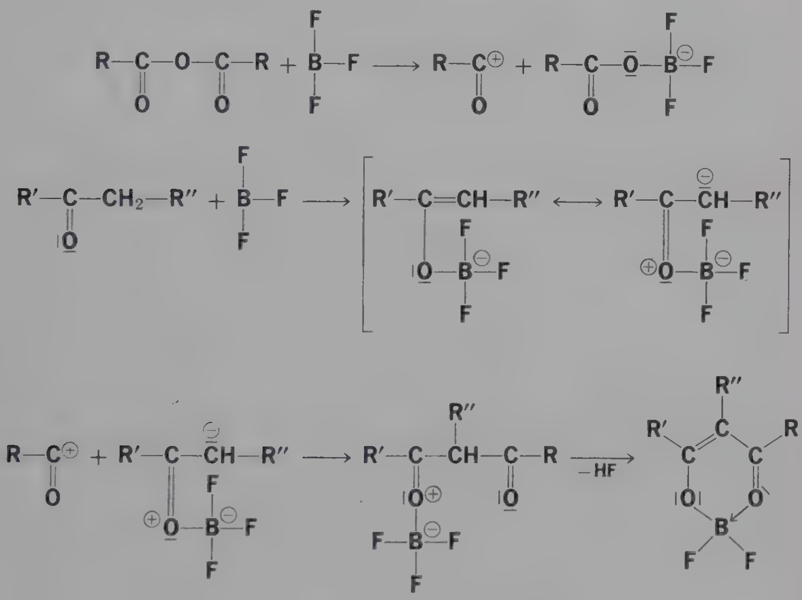
0-92 Acylation of ketones by anhydrides



---

[318] Treibs, Riemer, and Orttmann, *Chem. Ber.* **93**, 551 (1960).

Acylation of $Z{-}\overset{\ominus}{\bar{C}}H{-}Z'$ by anhydrides, comparable to their acylation by acyl halides (**0-91**), is not often carried out. A much more common reaction is acylation of ketones by anhydrides, with boron trifluoride as catalyst,[319] to give β-diketones. The actual product is a complex containing BF_2, which may be decomposed by aqueous sodium acetate to give the acylated ketone. Therefore one mole of boron trifluoride is required for each mole of ketone. The boron trifluoride plays a double role in the mechanism. It assists in ionization of the anhydride (an S_N1 type of process), and converts the ketone into a boron derivative of the enolate:



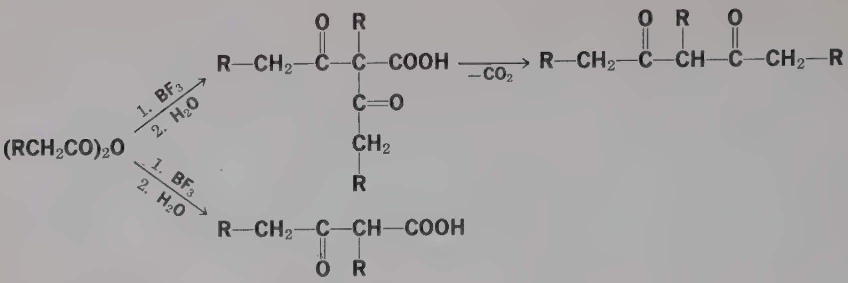
With respect to the ketone, this is an electrophilic substitution, with a mechanism similar to that of the bromination of ketones (reaction **2-4**, p. 458). There is evidence that at least in some cases the enol is first O-acylated, and then the resulting enol ester is attacked by another acyl cation to give the β-diketone. Indeed, enol esters obtained in other ways may be converted to β-diketones in a similar manner. With unsymmetrical ketones, acylation occurs chiefly on the more highly substituted side.

A side reaction is self-condensation of the anhydride, providing it has an α hydrogen, to give either a β-diketone or a β-keto acid. In the former case, decarboxylation takes place (see reaction **2-26**, p. 477). Of course, the β-keto acid may also be decarboxylated. These reactions are examples of acylation of anhydrides by anhydrides and are sometimes used as preparative methods. In the latter process, an anhydride is converted to a symmetrical ketone (after decarboxylation of the β-keto acid):[320]

---

[319] For a review, see Hauser, Swarmer, and Adams, *Org. Reactions* **8**, 59–196 (1954), pp. 98–106.

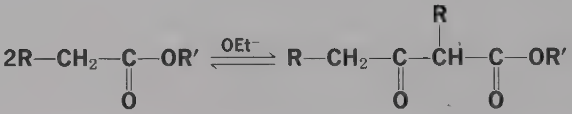
[320] See Musso and Figge, *Ann.* **668**, 1, 15 (1963).



Another means of accomplishing essentially the same result is discussed at reaction **0-98.** Mixed carboxylic-carbonic anhydrides can react with magnesium enolates to give β-keto esters.[321]

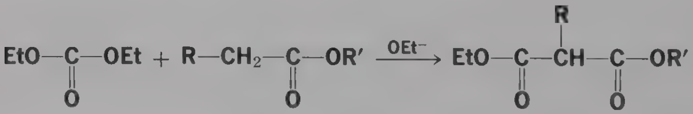
OS **III,** 16.

0-93 Acylation of esters by esters. The Claisen and Dieckmann condensations



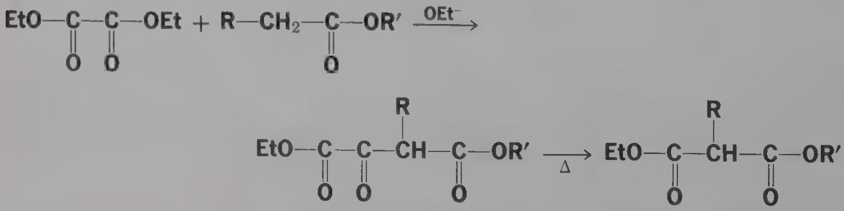
$$2R{-}CH_2{-}\underset{\substack{\|\\ O}}{C}{-}OR' \xrightleftharpoons{OEt^-} R{-}CH_2{-}\underset{\substack{\|\\ O}}{C}{-}\overset{\substack{R\\ |}}{CH}{-}\underset{\substack{\|\\ O}}{C}{-}OR'$$

When esters containing an α hydrogen are treated with a strong base such as sodium ethoxide, a condensation occurs, to give a β-keto ester. This reaction is called the *Claisen condensation.*[322] When the condensation is carried out with a mixture of two different esters, each of which possesses an α hydrogen, a mixture of all four products is generally obtained, and the reaction is seldom useful synthetically. However, if only one of the esters has an α hydrogen, then the mixed reaction is frequently satisfactory. Among esters lacking α hydrogens (hence acting as the substrate ester) which are commonly used in this way are esters of benzoic and other aromatic acids, and ethyl carbonate and ethyl oxalate. Ethyl carbonate gives malonic esters



$$EtO{-}\underset{\substack{\|\\ O}}{C}{-}OEt + R{-}CH_2{-}\underset{\substack{\|\\ O}}{C}{-}OR' \xrightarrow{OEt^-} EtO{-}\underset{\substack{\|\\ O}}{C}{-}\overset{\substack{R\\ |}}{CH}{-}\underset{\substack{\|\\ O}}{C}{-}OR'$$

while ethyl oxalate gives α-keto esters, which may then be decarbonylated (reaction **0-13**) to the same malonic esters.



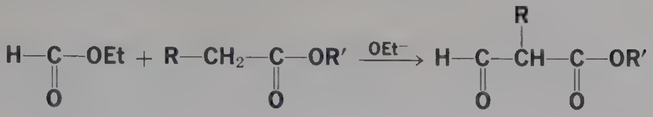
$$EtO{-}\underset{\substack{\|\\ O}}{C}{-}\underset{\substack{\|\\ O}}{C}{-}OEt + R{-}CH_2{-}\underset{\substack{\|\\ O}}{C}{-}OR' \xrightarrow{OEt^-} EtO{-}\underset{\substack{\|\\ O}}{C}{-}\underset{\substack{\|\\ O}}{C}{-}\overset{\substack{R\\ |}}{CH}{-}\underset{\substack{\|\\ O}}{C}{-}OR' \xrightarrow[\Delta]{} EtO{-}\underset{\substack{\|\\ O}}{C}{-}\overset{\substack{R\\ |}}{CH}{-}\underset{\substack{\|\\ O}}{C}{-}OR'$$

---

[321] Bram and Vilkas, *Bull. Soc. chim. France* **1964,** 945.

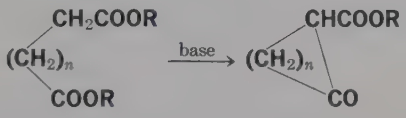
[322] For a review, see Hauser and Hudson, *Org. Reactions* **1,** 266–302 (1942).

Ethyl formate serves to introduce the formyl group:



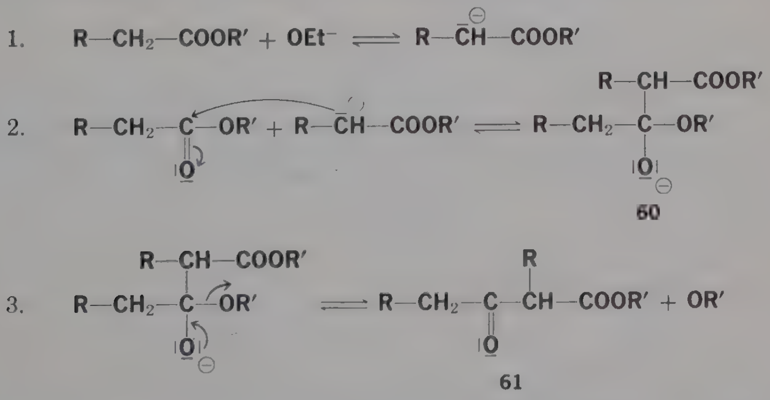
$$\mathrm{H{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OEt + R{-}CH_2{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OR' \xrightarrow{OEt^-} H{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}\overset{\displaystyle R}{\overset{|}{C}H}{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OR'}$$

When the two ester groups involved in the condensation are in the same molecule, the product is a cyclic β-keto ester, and the reaction is called the *Dieckmann condensation.*[323]



The Dieckmann condensation is most successful for the formation of five-, six-, and seven-membered rings. Yields for rings of nine to twelve members are very low or nonexistent; larger rings may be closed with high-dilution techniques. Reactions in which large rings are to be closed are generally assisted by high dilution, since one end of the molecule has a better chance of finding the other end than of finding another molecule.

The mechanism of the Claisen and the Dieckmann reactions is the ordinary tetrahedral mechanism, with one molecule of ester being converted to a nucleophile by the base, and the other serving as the substrate.



$$1.\quad \mathrm{R{-}CH_2{-}COOR' + OEt^- \rightleftharpoons R{-}\overset{\ominus}{\bar{C}}H{-}COOR'}$$

$$2.\quad \mathrm{R{-}CH_2{-}\underset{|\underline{O}}{\underset{\|}{C}}{-}OR' + R{-}\bar{C}H{-}COOR' \rightleftharpoons R{-}CH_2{-}\overset{\displaystyle R{-}CH{-}COOR'}{\overset{|}{\underset{|\underline{O}|^{\ominus}}{\underset{|}{C}}}}{-}OR'}$$

60

$$3.\quad \mathrm{R{-}CH_2{-}\overset{\displaystyle R{-}CH{-}COOR'}{\overset{|}{\underset{|\underline{O}|^{\ominus}}{\underset{|}{C}}}}{-}OR' \rightleftharpoons R{-}CH_2{-}\underset{|\underline{O}}{\underset{\|}{C}}{-}\overset{\displaystyle R}{\overset{|}{C}H}{-}COOR' + OR'}$$

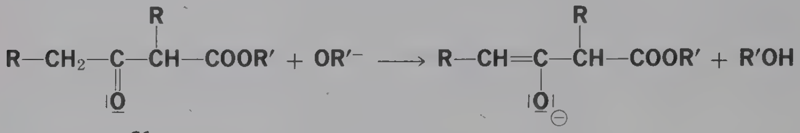
61

This reaction illustrates the striking difference in behavior between esters on the one hand and aldehydes and ketones on the other. When a carbanion such as an enolate ion is added to the carbonyl group of an aldehyde or ketone (reaction **6-41,** p. 697), the H or R is not lost, since these groups are much poorer leaving groups than OR. Instead the intermediate similar to **60** adds a proton at the oxygen to give a hydroxy compound.

In contrast to reaction **0-86,** ordinary esters react quite well; that is, two Z groups are not needed. A lower degree of acidity is satisfactory because it is not necessary to convert the attacking ester entirely to its ion. Step 1, the conversion of the ester to its ion, is an equilibrium reaction, and the equilibrium lies well over to the left. Nevertheless, the small amount of enolate ion formed is sufficient to attack the readily approachable ester substrate. In reaction **0-86** it is necessary to convert the reagent completely to its conjugate base. All the steps in the reaction are equilibria. The reaction proceeds because the product (**61**) is converted to its conjugate base by the base present:

---

[323] For a review, see Schaefer and Bloomfield, *Org. Reactions* **15,** 1–203 (1967).



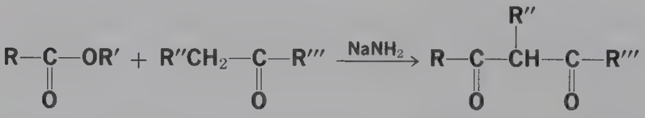
$$R{-}CH_2{-}\underset{\overset{\|}{O}}{C}{-}\overset{R}{\overset{|}{C}H}{-}COOR' + OR'^- \longrightarrow R{-}CH{=}\underset{\underset{O^{\ominus}}{|}}{C}{-}\overset{R}{\overset{|}{C}H}{-}COOR' + R'OH$$

61

The use of stronger bases, such as sodium amide or sodium hydride, often increases the yield. For some esters (for example, $Me_2CHCOOEt$) stronger bases *must* be used, since sodium ethoxide is ineffective.

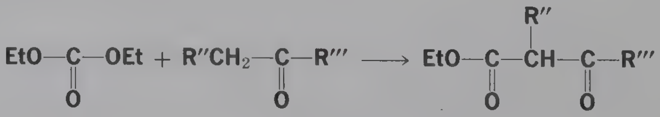
OS **I,** 235; **II,** 116, 194, 272, 288; **III,** 231, 300, 379, 510; **IV,** 141; **44,** 67, 86.

0-94 Acylation of ketones and nitriles by esters



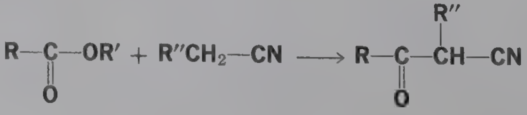
$$R{-}\underset{\overset{\|}{O}}{C}{-}OR' + R''CH_2{-}\underset{\overset{\|}{O}}{C}{-}R''' \xrightarrow{NaNH_2} R{-}\underset{\overset{\|}{O}}{C}{-}\overset{R''}{\overset{|}{C}H}{-}\underset{\overset{\|}{O}}{C}{-}R'''$$

Esters may be treated with ketones to give β-diketones, in a reaction which is essentially the same as reaction **0-93.**[322] The reaction is so similar that it is sometimes also called the Claisen condensation, though this usage is unfortunate. A fairly strong base, such as sodium amide or sodium hydride, is required. Esters of formic acid R = H give β-keto aldehydes. Ethyl carbonate gives β-keto esters.



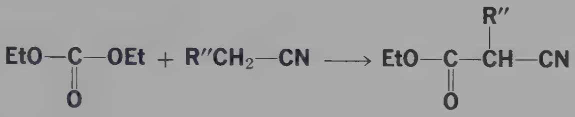
$$EtO{-}\underset{\overset{\|}{O}}{C}{-}OEt + R''CH_2{-}\underset{\overset{\|}{O}}{C}{-}R''' \longrightarrow EtO{-}\underset{\overset{\|}{O}}{C}{-}\overset{R''}{\overset{|}{C}H}{-}\underset{\overset{\|}{O}}{C}{-}R'''$$

In the case of unsymmetrical ketones, the attack usually comes from the less highly substituted side, so that CH_3 is more reactive than RCH_2, and the R_2CH group rarely attacks. This is in sharp contrast to reaction **0-92,** and the two reactions are thus complementary. As in the case of reaction **0-93,** this reaction has been used to effect cyclization, especially to prepare five- and six-membered rings. Nitriles are frequently used instead of ketones, the products being β-keto nitriles.



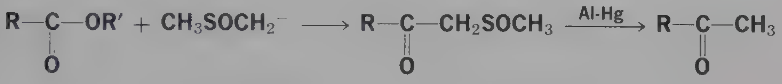
$$R{-}\underset{\overset{\|}{O}}{C}{-}OR' + R''CH_2{-}CN \longrightarrow R{-}\underset{\overset{\|}{O}}{C}{-}\overset{R''}{\overset{|}{C}H}{-}CN$$

Similarly, α-cyano esters may be obtained upon treatment of ethyl carbonate with nitriles.



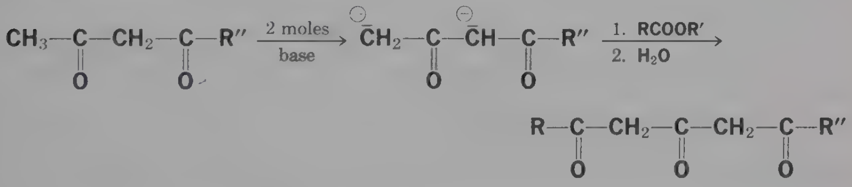
$$\mathrm{EtO{-}\underset{\underset{O}{\|}}{C}{-}OEt + R''CH_2{-}CN \longrightarrow EtO{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R''}{|}}{C}H{-}CN}$$

Other carbanionic groups, such as acetylide ions, and ions derived from α-methylpyridines have also been used as nucleophiles. A particularly useful nucleophile is $CH_3SOCH_2^-$,[324] the conjugate base of dimethyl sulfoxide, since the β-keto sulfoxide produced can easily be reduced to a methyl ketone, in high yields, with aluminum amalgam.



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}OR' + CH_3SOCH_2^- \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}CH_2SOCH_3 \xrightarrow{Al\text{-}Hg} R{-}\underset{\underset{O}{\|}}{C}{-}CH_3}$$

As in reaction **0-86**, a ketone attacks with its second most acidic position if two moles of base are used. Thus, β-diketones have been converted to 1,3,5-triketones:[325]

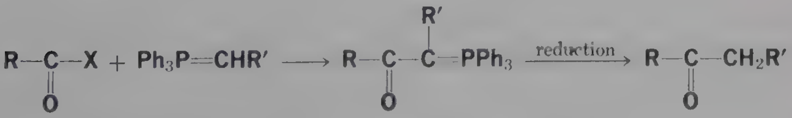


$$\mathrm{CH_3{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}R'' \xrightarrow[\text{base}]{\text{2 moles}} \overset{\ominus}{\bar{C}}H_2{-}\underset{\underset{O}{\|}}{C}{-}\overset{\ominus}{\bar{C}}H{-}\underset{\underset{O}{\|}}{C}{-}R'' \xrightarrow[2.\ H_2O]{1.\ RCOOR'} R{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}R''}$$

Side reactions are condensation of the ketone with itself (reaction **6-39,** p. 692), of the ester with itself (reaction **0-93**), and of the ketone with the ester, but with the ester supplying the α position (reaction **6-40,** p. 696). The mechanism is the same as in reaction **0-93.**[326]

OS **I,** 238; **II,** 126, 200, 287, 487, 531; **III,** 17, 251, 291, 387, 829; **IV,** 174, 210, 461, 536; **43,** 40; **46,** 57.

0-95 Acylation of phosphoranes



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}X + Ph_3P{=}CHR' \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R'}{|}}{C}{=}PPh_3 \xrightarrow{\text{reduction}} R{-}\underset{\underset{O}{\|}}{C}{-}CH_2R'}$$

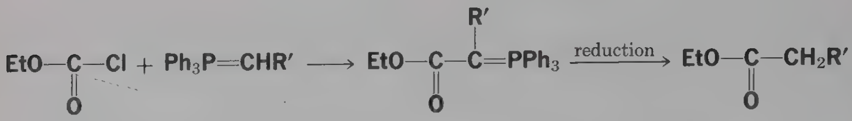
Acyl halides, esters, and certain other acid derivatives react with phosphorus ylides (phosphoranes) containing an α hydrogen to give stable β-keto alkylidene phosphoranes, which may then be reduced to ketones.[327] Ethyl chloroformate similarly gives esters:

---

[324] Becker, Mikol, and Russell, *J. Am. Chem. Soc.* **85,** 3410 (1963); Becker and Russell, *J. Org. Chem.* **28,** 1896 (1963); Corey and Chaykovsky, *J. Am. Chem. Soc.* **86,** 1639 (1964).

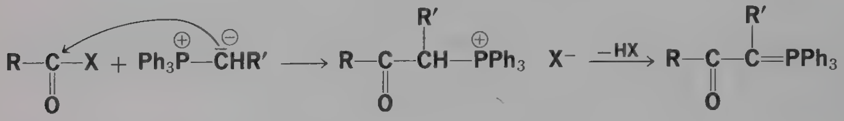
[325] Miles, Harris, and Hauser, *J. Org. Chem.* **30,** 1007 (1965); OS **46,** 57 (1966).

[326] Hill, Burkus, and Hauser, *J. Am. Chem. Soc.* **81,** 602 (1959).



$$\mathrm{EtO{-}\underset{\overset{\|}{O}}{C}{-}Cl + Ph_3P{=}CHR' \longrightarrow EtO{-}\underset{\overset{\|}{O}}{C}{-}\overset{\overset{R'}{|}}{C}{=}PPh_3 \xrightarrow{\text{reduction}} EtO{-}\underset{\overset{\|}{O}}{C}{-}CH_2R'}$$

The initial reaction product is a phosphonium salt, which loses HX:



$$\mathrm{R{-}\underset{\overset{\|}{O}}{C}{-}X + Ph_3\overset{\oplus}{P}{-}\overset{\ominus}{C}HR' \longrightarrow R{-}\underset{\overset{\|}{O}}{C}{-}\overset{\overset{R'}{|}}{C}H{-}\overset{\oplus}{P}Ph_3\ \ X^- \xrightarrow{-HX} R{-}\underset{\overset{\|}{O}}{C}{-}\overset{\overset{R'}{|}}{C}{=}PPh_3}$$

0-96 Preparation of acyl cyanides

$$\mathrm{RCOX + CuCN \longrightarrow RCOCN}$$

Acyl cyanides may be prepared by treatment of acyl halides with copper cyanide. The mechanism is not known and might be free-radical or nucleophilic substitution.

OS **III**, 112.

0-97 Preparation of diazo ketones

$$\mathrm{RCOX + CH_2N_2 \longrightarrow RCOCHN_2}$$

The reaction between acyl halides and diazomethane is of wide scope, and is the best way to prepare diazo ketones.[328] Diazomethane must be present in excess, or the HX produced will react with the diazo ketone (reaction **0-67**). This reaction is the first step of the Arndt-Eistert synthesis (reaction **8-8**, p. 809).

OS **III**, 119.

0-98 Ketonic decarboxylation

$$\mathrm{2RCOOH \xrightarrow[ThO_2]{400\text{–}500°} RCOR + CO_2}$$

Carboxylic acids may be converted to symmetrical ketones by pyrolysis in the presence of thorium oxide. An alternative method involves heating of the ferrous salt of the acid.[329] Although many books assert that ketones are prepared by heating calcium or barium salts of acids, in reality this reaction gives very low yields.[330] However, methyl ketones have been prepared by heating barium acetate with barium salts of other acids, in an example of a mixed process. In another mixed reaction, formic acid and another acid, heated over thorium oxide, give aldehydes. Mixed alkyl aryl ketones have been prepared by heating mixtures of ferrous salts.[331] When the R group is large, the methyl ester rather than the acid can be decarbmethoxylated over thorium oxide to give the symmetrical ketone.

---

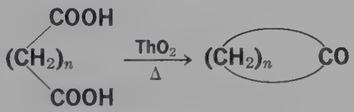
[327] For a review, see Trippett, *Quart. Rev.* (*London*) **17**, 406–440 (1964), pp. 424–426.

[328] For a review, see Eistert, in "Newer Methods of Preparative Organic Chemistry," vol. 1, pp. 513–570, Interscience Publishers, Inc., New York, 1948.

[329] Davis and Schultz, *J. Org. Chem.* **27**, 854 (1962).

[330] Schultz and Sichels, *J. Chem. Educ.* **38**, 300 (1961).

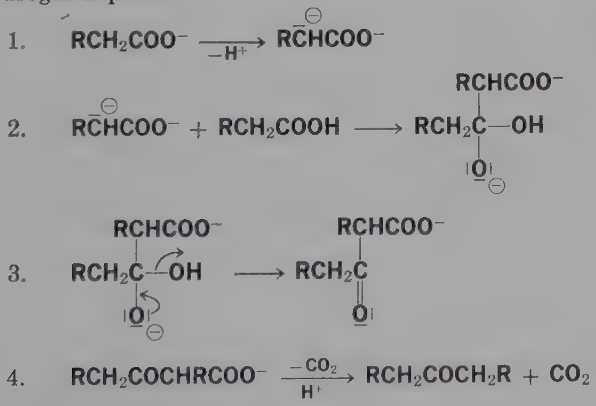
The reaction has been performed on dicarboxylic acids, whereupon cyclic ketones are obtained:



This process, called the *Ruzicka cyclization,* is good for the preparation of rings of six and seven members and, with lower yields, of eight members. In contrast to the lack of success with monocarboxylic acids, calcium and barium salts of dicarboxylic acids may be heated to give cyclic ketones of large rings (C_9 to C_{19}) as well as of five-, six-, and seven-membered rings.

Not much work has been done on the mechanism of this reaction. On the basis of ^{14}C labeling experiments, two mechanisms have been proposed, one for the case where an α hydrogen is present and one for the case where it is not:[332]

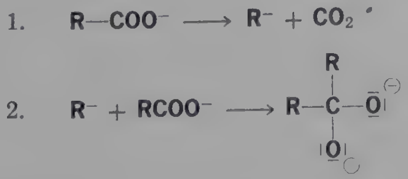
Where α hydrogen is present



$$RCH_2COO^- \xrightarrow[-H^+]{} R\overset{\ominus}{C}HCOO^-$$

$$RCH_2COCHRCOO^- \xrightarrow[H^+]{-CO_2} RCH_2COCH_2R + CO_2$$

Where α hydrogen is not present

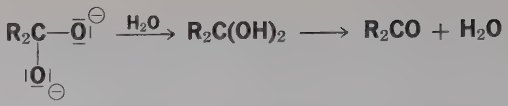


$$R{-}COO^- \longrightarrow R^- + CO_2$$

---

[331] Granito and Schultz, *J. Org. Chem.* **28,** 879 (1963).

[332] Ötvos and Noszkó, *Tetrahedron Letters* **1960,** No. 2, 19.

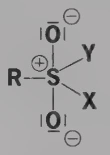
3. 

$$\mathrm{R_2\underset{|\underline{O}|^{\ominus}}{C}-\overline{\underline{O}}|^{\ominus} \xrightarrow{H_2O} R_2C(OH)_2 \longrightarrow R_2CO + H_2O}$$

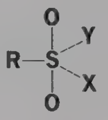
Each of these mechanisms involves tetrahedral nucleophilic substitution. The steps involving loss of CO_2 (steps 4 and 1, respectively) are similar to decarboxylation reactions considered in Chapter 12 (reaction **2-26**, p. 477).

OS **I**, 192; **II**, 389; **IV**, 854. Also see OS **IV**, 555, 560.

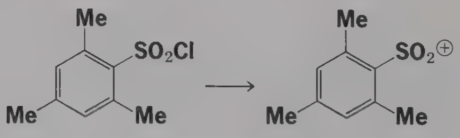
Nucleophilic Substitution at a Sulfur Atom. Nucleophilic substitution at RSO_2X is similar to attack at RCOX. Many of the reactions are essentially the same, although sulfonyl halides are not as active as halides of carboxylic acids. The actual mechanisms are not identical, because a "tetrahedral" intermediate in this case (**62**) would have five groups on the central atom.[333] Although this is possible, since sulfur can accommodate up to 12 electrons in its valence shell, it seems more likely that these mechanisms more closely resemble the S_N2 mechanism, that is, involve a transition state something like **63**, but not necessarily with backside attack. At least in the case of acid and basic hydrolysis of aryl arenesulfonates, it has been shown by the use of ^{18}O that an intermediate like **62** is not reversibly formed, since ester recovered when the reaction was stopped before completion contained no ^{18}O when the hydrolysis was carried out in the presence of labeled water.[334] In some cases S_N1-type mechanisms have been shown; for example, the intermediate **64** has been shown to arise in nucleophilic substitution of mesitylenesulfonyl chloride:[335]



62



63



64

However, less work has been done on the mechanism of these substitutions than on those at an acyl carbon.

Backside attack at a *divalent* sulfur has been shown in the exchange reac-

[333] For a review, see Vizgert, *Russ. Chem. Rev.* **32,** 1–20 (1963).

[334] Christman and Oae, *Chem. Ind.* (*London*) **1959,** 1251; Oae, Fukumoto, and Kiritani, *Bull. Chem. Soc. Japan* **36,** 346 (1963).

[335] Ref. 333, p. 14.

tion between Bunte salts ($R—S—SO_3^-$) and sulfite ions ($SO_3^=$), by the demonstration that branching in R greatly retards the rate.[336]

In the special case of nucleophilic substitution at a sulfonic ester, RSO_2OR', where R′ is alkyl, R′—O cleavage is much more likely than S—O cleavage, because the OSO_2R group is such a good leaving group (p. 294). Many of these reactions have been considered previously (e.g., reactions **0-4, 0-18,** etc.) because they are nucleophilic substitutions at an alkyl carbon atom, and not at a sulfur atom. However, when R′ is aryl, then the S—O bond is much more likely to cleave because of the very low tendency which aryl substrates have for nucleophilic substitution.[337]

0-99 Attack by OH. Hydrolysis of sulfonic acid derivatives

$$RSO_2Cl \xrightarrow[H^+]{H_2O} RSO_2OH$$

$$RSO_2OR' \xrightarrow[H^+]{H_2O} RSO_2OH$$

$$RSO_2NR'_2 \xrightarrow[H^+]{H_2O} RSO_2OH$$

Sulfonyl chlorides, and esters and amides of sulfonic acids may be hydrolyzed to the corresponding acids. Sulfonyl chlorides are usually hydrolyzed with acids, although water alone is sometimes sufficient. Basic catalysis is also used, although the salt, of course, is the product obtained here. Esters are readily hydrolyzed, many with water or dilute alkali. This is actually the same reaction as **0-4,** and usually involves R′—O cleavage, except when R′ is aryl. However, in some cases retention of configuration has been shown at alkyl R′, indicating S—O cleavage in these cases.[338] Sulfonamides are generally not hydrolyzed by alkaline treatment, not even with hot concentrated alkali,[339] but acids hydrolyze them, though less readily than they do sulfonyl halides or sulfonic esters. Of course, ammonia or the amine appears as the salt.

OS **I,** 14; **II,** 471; **III,** 262; **IV,** 34. Also see OS **46,** 51.

0-100 Attack by OR. Formation of sulfonic esters

$$RSO_2Cl + R'OH \xrightarrow{\text{base}} RSO_2OR'$$

$$RSO_2NR''_2 + R'OH \xrightarrow{\text{base}} RSO_2OR' + NHR''_2$$

Sulfonic esters are most frequently prepared by treatment of the corresponding halides with alcohols. Both R and R′ may be alkyl or aryl. The reaction with sulfonamides has been much less often used and is limited to N,N-disubstituted sulfonamides; that is, R″ may not be hydrogen. However, within these limits it is a useful reaction.[339] The nucleophile in this case is actually $R'O^-$. However, R'' may be hydrogen (as well as alkyl) if the nucleophile is a phenol, so that the product is RSO_2OAr. Acidic catalysts are used in this case.[340]

---

[336] Fava and Iliceto, *J. Am. Chem. Soc.* **80,** 3478 (1958). Also see Ref. 8.

[337] See, for example, Oae, Fukumoto, and Kiritani, *Bull. Chem. Soc. Japan* **36,** 346 (1963); Oae and Kiritani, *Bull. Chem. Soc. Japan* **38,** 765 (1965).

[338] Chang, *Tetrahedron Letters* **1964,** 305.

[339] For a review, see Searles and Nukina, *Chem. Rev.* **59,** 1077–1103 (1959).

OS **I,** 145; **III,** 366; **IV,** 753. Also see OS **IV,** 529.

0-101 Attack by ammonia or amines. Formation of sulfonamides

$$RSO_2Cl + NH_3 \longrightarrow RSO_2NH_2$$

The treatment of sulfonyl chlorides with ammonia or amines is the usual way of preparing sulfonamides. Primary amines give N-alkyl sulfonamides, and secondary amines give N,N-dialkyl sulfonamides. The reaction is the basis of the *Hinsberg test* for distinguishing between primary, secondary, and tertiary amines. N-Alkyl sulfonamides, having an acidic hydrogen, are soluble in alkali, while N,N-dialkyl sulfonamides are not. Since tertiary amines give no reaction with sulfonyl chlorides, primary, secondary, and tertiary amines may be told apart. However, the test is limited, since N-alkyl sulfonamides in which the alkyl group has six or more carbons are insoluble in alkali despite their acidic hydrogen.[341] Sulfonamides can also be prepared from other sulfonamides in a transamination reaction.[339]

OS **IV,** 34, 943; **40,** 93.

0-102 Attack by halogen. Formation of sulfonyl halides

$$RSO_2OH + PCl_5 \longrightarrow RSO_2Cl$$

This reaction, parallel with reaction **0-70,** is the standard method for the preparation of sulfonyl halides. Also used are PCl_3 and $SOCl_2$, and sulfonic acid salts may also serve as substrates. Sulfonyl bromides have been prepared from sulfonyl hydrazides ($ArSO_2NHNH_2$, themselves prepared by reaction **0-101**) by treatment with bromine in aqueous acid.[342]

OS **I,** 84; **IV,** 571, 693, 846, 937.

0-103 Attack by hydrogen. Reduction of sulfonyl chlorides

$$2RSO_2Cl + Zn \longrightarrow (RSO_2)_2Zn \xrightarrow{H^+} 2RSO_2H$$

Sulfinic acids may be prepared by reduction of sulfonyl chlorides.[343] Although mostly done on aromatic sulfonyl chlorides, the reaction has also been applied to alkyl compounds. Besides zinc, sodium sulfite, hydrazine, sodium sulfide, and other reducing agents have been used. For reduction of sulfonyl chlorides to mercaptans, see reaction **9-47,** page 900.

OS **I,** 7, 492; **IV,** 674.

---

[340] Klamann and Fabienke, *Chem. Ber.* **93,** 252 (1960).

[341] Fanta and Wang, *J. Chem. Educ.* **41,** 280 (1964).

[342] Poshkus, Herweh, and Magnotta, *J. Org. Chem.* **28,** 2766 (1963).

[343] For a review, see Truce and Murphy, *Chem. Rev.* **48,** 69–124 (1951), pp. 69–83.

0-104 Attack by carbon. Preparation of sulfones

$$ArSO_2Cl + Ar'MgX \longrightarrow ArSO_2Ar'$$

Grignard reagents convert aromatic sulfonyl chlorides to sulfones. Esters of aromatic sulfonic acids may also serve as substrates.

CHAPTER ELEVEN

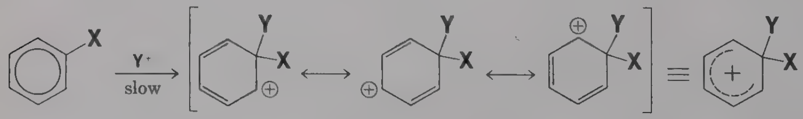
Aromatic Electrophilic Substitution

Most substitutions at an aliphatic carbon are nucleophilic. In aromatic systems the situation is reversed because the high electron density at the aromatic ring attracts positive species and not negative ones. In an electrophilic substitution the attacking species is a positive ion or the positive end of a dipole or induced dipole. The leaving group must necessarily depart without its electron pair. In nucleophilic substitutions, the chief leaving groups are those best able to carry the unshared pair: Br^-, H_2O, $OCOR^-$, OTs^-, etc., that is, the weakest bases. In electrophilic substitutions, the most important leaving groups are those which can best exist without the pair of electrons necessary to fill the outer shell, that is, the weakest Lewis acids. The most common leaving group in electrophilic aromatic substitutions is the proton.

MECHANISM

Electrophilic aromatic substitutions are unlike nucleophilic substitutions in that the large majority proceed by just one mechanism, with respect to the substrate.[1] The attacking species may be produced in various ways, often in several different ways even for the same reaction, and the same reaction may have different attacking species under different conditions, but what is happening to the aromatic ring is basically the same in all cases. For this reason most attention in the study of aromatic electrophilic substitution mechanisms centers around the identity of the attacking entity and how it is produced.[2]

The electrophile may be a positive ion or a dipole. If it is a positive ion, it attacks the ring, removing a pair of electrons from the sextet, to give a carbonium ion:



1

2

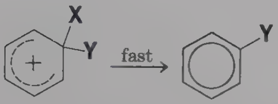
which is a resonance hybrid, as shown in **1**, and is frequently represented as in **2**. Ions of this type are called *σ-complexes*. It may easily be seen that the great stability associated with an aromatic sextet is no longer present in **1**, although the ion is stabilized by resonance of its own. The σ-complex is generally a highly reactive intermediate and must stabilize itself by a further reaction, though it has been isolated (see p. 379).

---

[1] For monographs, see Norman and Taylor, "Electrophilic Substitution in Benzenoid Compounds," American Elsevier Publishing Company, New York, 1965; and de la Mare and Ridd, "Aromatic Substitution—Nitration and Halogenation," Academic Press Inc., New York, 1959.

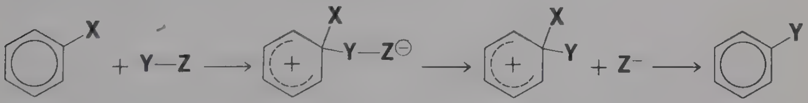
[2] For a review of the mechanism of the substitution process itself, see Berliner, *Progr. Phys. Org. Chem.* **2**, 253–321 (1964).

Carbonium ions may stabilize themselves in various ways (see p. 141), but for an ion of this type the most likely way is by loss of either X^+ or Y^+, since the aromatic sextet will then be restored, and in fact this is the second step of the mechanism:



The second step is nearly always faster than the first, so that the first is rate-determining and the reaction is second order (unless the *formation* of the attacking species is slower still, in which case the aromatic compound does not take part in the rate expression at all). If Y^+ is lost, then there is no net reaction, but if X^+ is lost, an aromatic substitution has taken place. If X^+ is a proton, then a base is necessary to help remove it.

If the attacking species is not an ion, but a dipole, then the product must have a negative charge, unless a part of the dipole, with its pair of electrons, is broken off somewhere in the process, e.g.,



The mechanism we have outlined is sometimes called the S_E2 mechanism (because it is bimolecular), but in this book we shall reserve that name for aliphatic substrates (see Chapter 12) and shall refer to the present mechanism as the *σ-complex mechanism.* It may be noted that mechanisms corresponding to the S_N1, in which the leaving group comes off first and then the attacking species enters, are rare in aromatic electrophilic substitutions, being found only in certain cases in which carbon is the leaving atom (see reactions **1-39**, **1-40**, and **1-43**) or when a very strong base is present (see reaction **1-1**). Note also that simultaneous attack and departure mechanisms (corresponding to S_N2) are not found at all. An addition-elimination mechanism has been postulated in one case (see reaction **1-6**).

The questions as to what the attacking entity is in each case, and how it is formed, will be discussed for each reaction in the reactions section of this chapter.

The evidence for the σ-complex mechanism is mainly of two kinds:

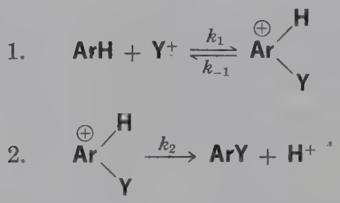
1. *Isotope effects.*[3] If the hydrogen ion departed before the arrival of the electrophile (S_E1 mechanism) or if the arrival and departure were simulta-

---

[3] For reviews of hydrogen isotope effects in aromatic substitutions, see Zollinger, *Advan. Phys. Org. Chem.* **2**, 163–200 (1964); and Ref. 2, pp. 281–294.

neous, then there should be a substantial isotope effect (that is, deuterated substrates should undergo substitution more slowly than nondeuterated compounds), because, in each case, the C—H bond is broken in the rate-determining step. However, in the σ-complex mechanism, the C—H bond is not broken in the rate-determining step, and so no isotope effect should be found. Many such studies have been carried out, and in most cases, especially in the case of nitrations, there is no isotope effect.[4] This result is incompatible with either the S_E1 or the simultaneous mechanism.

However, in many instances isotope effects have been found. Since the values are generally much lower than we would expect for either the S_E1 or the simultaneous mechanisms (for example, 1 to 3 for k_H/k_D instead of 6 to 7), we must look elsewhere for the explanation. For the case where hydrogen is the leaving group, the σ-complex mechanism may be summarized:



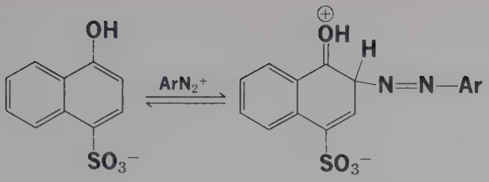
Isotope effects can arise from this mechanism in at least two ways. If the second step has a rate comparable to or less than the first ($k_2[\mathrm{ArHY}^+] \overset{\approx}{<} k_1[\mathrm{ArH}][\mathrm{Y}^+]$), then there will obviously be an isotope effect. However, it is probable that most isotope effects in aromatic substitutions are not caused by this circumstance and that the first step is generally much slower than the second. It is likely that most isotope effects arise from the reversibility of step 1, by a *partitioning effect.* The rate at which ArHY^+ reverts to ArH should be essentially the same as that at which ArDY^+ (or ArTY^+) reverts to ArD (or ArT), since the Ar—H bond is not cleaving. However, ArHY^+ should go to ArY faster than either ArDY^+ or ArTY^+, since the Ar—H bond is broken in this step. If $k_2 \gg k_{-1}$, this does not matter: since a large majority of the intermediates go to product, the rate is determined only by the slow step ($k_1[\mathrm{ArH}][\mathrm{Y}^+]$), and no isotope effect is predicted. However, if $k_2 \overset{\approx}{<} k_{-1}$, then the reversion to starting materials is important. If k_2 for ArDY^+ (or ArTY^+) is less than k_2 for ArHY^+, but k_{-1} is the same, then a larger proportion of ArDY^+ reverts to starting compounds. That is, k_2/k_{-1} (*the partition factor*) for ArDY^+ is less than that for ArHY^+. Consequently, the reaction is slower for ArD than for ArH, and an isotope effect is observed.

One circumstance which could affect the k_2/k_{-1} ratio is steric hindrance. Thus, diazonium coupling of **3** gave no isotope effect, while coupling of **5** gave a k_H/k_D ratio of 6.55.[5] For steric reasons it is much easier for **6** to lose $\mathrm{ArN_2}^+$ than it is for **4**, so that k_{-1} is greater for the latter, while k_2 is about the same for each. In this case the partition factor is sufficiently different

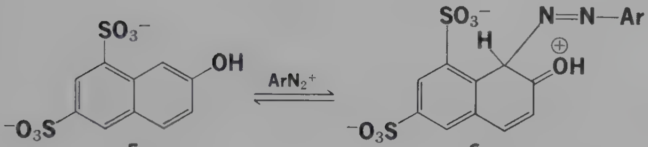
---

[4] The pioneering studies were by Melander: Melander, *Arkiv Kemi* **2**, 211 (1950); Berglund-Larsson and Melander, *Arkiv Kemi* **6**, 219 (1953). Zollinger, in Ref. 3, presents a table of isotope-effect results.

[5] Zollinger, *Helv. Chim. Acta* **38**, 1597, 1617, 1623 (1955).



3 **4**



5 **6**

for **4** and **6** that **5** exhibits a large isotope effect and **3** exhibits none. Another factor which affects partitioning is the base concentration. An increasing concentration of base increases the rate at which the intermediate goes to product without affecting the rate at which it reverts to starting materials.

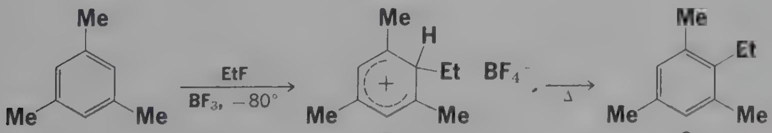
Small isotope effects can also arise in other ways (for example, in the step $ArXH^+ \longrightarrow ArH$ there may be a *secondary* isotope effect), and not all of the results are fully understood.

Evidence for the σ-complex mechanism has also been obtained from another kind of isotope-effect experiment, involving substitutions of the type

$$ArMR_3 + H_3O^+ \longrightarrow ArH + R_3MOH_2^+$$

where M was Si, Ge, Sn, or Pb, and R was methyl or ethyl. In these reactions the proton is the electrophile. If the σ-complex mechanism is operating, then the use of D_3O^+ should give rise to an isotope effect, since the D—O bond would be broken in the rate-determining step. Isotope effects of 1.55 to 3.05 were obtained,[6] in accord with the σ-complex mechanism.

2. *Isolation of σ-complex intermediates.* For a number of years attempts were made to isolate the σ-complex intermediate in order to provide convincing proof of the mechanism. This has now been done several times. For example, **7** was isolated as a solid, with melting point −15°, from treatment of



7 **8**

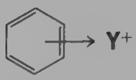
mesitylene with ethyl fluoride and the catalyst BF_3 at −80°. When **7** was heated, the normal substitution product, **8**, was obtained.[7]

---

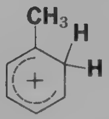
[6] Bott, Eaborn, and Greasley, *J. Chem. Soc.* **1964**, 4803.

[7] Olah and Kuhn, *J. Am. Chem. Soc.* **80,** 6541 (1958). For other examples see Ershov and Volod'kin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1962**, 680; and Olah, Noszko, and Pavlath, *Nature* **179,** 146 (1957).

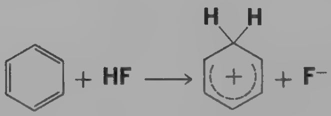
In Chapter 3 it was mentioned that positive ions can form addition complexes with π systems. Since the initial step of electrophilic substitution involves attack by a positive ion on an aromatic system, it is possible that such a complex, called a *π-complex* (to distinguish it from the σ-complex previously discussed), is formed before the electrophile actually removes the electron pair from the ring. Such a complex, which may be represented



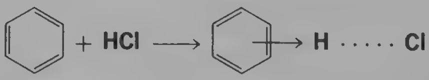
would represent an energy minimum on the reaction path. If the leaving group formed a similar complex before it finally left the environment of the ring, then the energy profile of the reaction would appear as in Figure 1 or 2, depending on the stability of the π-complexes. The stabilities of π-complexes (with Ag^+, Br_2, I_2, picric acid, HCl, etc.) and the stabilities of σ-complexes, e.g.,



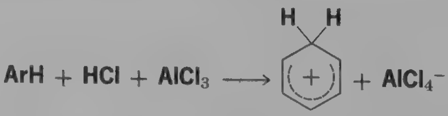
are known for many substituted benzenes. Table 1 presents a list of some of these values. The σ-complex stabilities were determined by relative basicity of the substrate toward HF:[8]



The π-complex stabilities in Table 1 are relative equilibrium constants for the reaction[9]



It is known that π-complexes are formed when aromatic hydrocarbons are treated with HCl alone, but that the use of HCl plus a Lewis acid gives σ-complexes:



---

[8] Kilpatrick and Luborsky, *J. Am. Chem. Soc.* **75**, 577 (1953). For a review of σ-complexes formed by the addition of a proton to an aromatic ring, see Perkampus and Baumgarten, *Angew. Chem. Intern. Ed. Engl.* **3**, 776–783 (1964). For a review of the basicity of aromatic compounds, see Perkampus, *Advan. Phys. Org. Chem.* **4**, 195–304 (1966).

[9] Brown and Brady, *J. Am. Chem. Soc.* **74**, 3570 (1952).

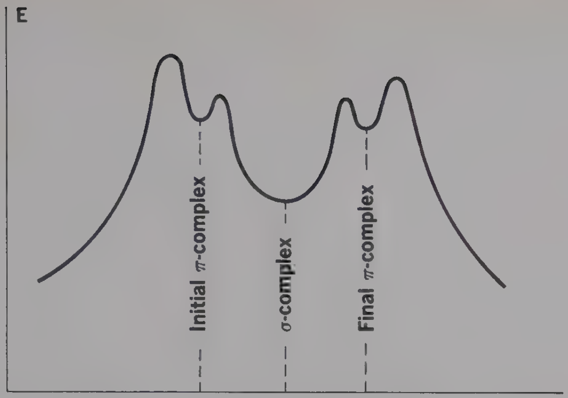


Figure 1. *Energy profile for an aromatic substitution in which π-complex formation is rate-determining.*[10]

As is shown in Table 1, the relative stabilities of the two types of complex are very different, the π-complex stability changing very little with methyl substitution, but the σ-complex stability changing a great deal. One way to determine which complex is rate-determining in a given reaction is to compare the relative rates of substitution with the relative stabilities of the two types of complex.[11] When this is done, it is found in most cases that the relative rates are similar to the σ-complex and not the π-complex stabilities. For example, Table 1 lists relative chlorination rates.[9] Similar results were obtained in room-temperature bromination with Br_2 in acetic acid,[12] and in acetylation with $CH_3CO^+ \quad SbF_6^-$.[13]

[10] From Olah, Kuhn, and Flood, *J. Am. Chem. Soc.* **83**, 4571 (1961).
[11] Condon, *J. Am. Chem. Soc.* **74**, 2528 (1952).
[12] Brown and Stock, *J. Am. Chem. Soc.* **79**, 1421 (1957).
[13] Olah, Kuhn, Flood, and Hardie, *J. Am. Chem. Soc.* **86**, 2203 (1964).
[14] From de la Mare and Ridd, Ref. 1, p. 46.

Figure 2. *Energy profile for an aromatic substitution in which π-complex formation is not important.*[14]

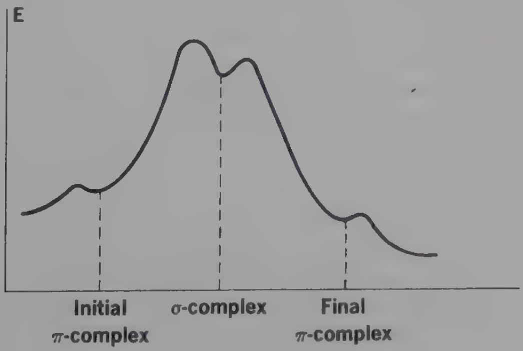


TABLE 1. Relative stabilities of σ- and π-complexes and relative rates of chlorination and nitration
In each case, p-xylene = 1.00

Substituents	*Relative σ-complex stability*[8]	*Relative π-complex stability*[9]	*Rate of chlorination*[9]	*Rate of nitration*[15]
None (benzene)	0.09	0.61	0.0005	0.51
Me	0.63	0.92	0.157	0.85
p-Me$_2$	1.00	1.00	1.00	1.00
o-Me$_2$	1.1	1.13	2.1	0.89
m-Me$_2$	26	1.26	200	
1,2,4-Me$_3$	63	1.36	340	
1,2,3-Me$_3$	69	1.46	400	
1,2,3,4-Me$_4$	400	1.63	2000	
1,2,3,5-Me$_4$	16,000	1.67	240,000	
Me$_5$	29,000		360,000	

However, in nitration with the powerful electrophile NO_2^+ (in the form of $NO_2^+ \quad BF_4^-$) the relative rates followed π-complex stabilities (Table 1).[15] Similar results were obtained upon bromination with Br_2 and $FeCl_3$ in nitromethane.[16] Other evidence for initial π-complex formation has also been found,[17] and it seems clear that this is the actual first step in aromatic electrophilic substitutions, though in most cases it is not rate-determining.

ORIENTATION AND REACTIVITY

Orientation and Reactivity in Substituted Benzene Rings.[18] When an electrophilic substitution reaction is performed on a monosubstituted benzene, the new group may be directed primarily to the ortho, meta, or para position, and the substitution may be slower or faster than with benzene itself. The group already on the ring determines which position the new group will take and whether the reaction will be slower or faster than with benzene. Groups which increase the reaction rate are called *activating,* and those which slow it, *deactivating.* Some groups are predominantly meta-directing; all of these are deactivating. Others are mostly ortho-para-directing; some of these are deactivating too, but most are activating. The groups direct *predominantly,* but usually not *exclusively.* For example, nitration of nitroben-

[15] Olah, Kuhn, and Flood, *J. Am. Chem. Soc.* **83**, 4571, 4581 (1961). Also see Ritchie and Win, *J. Org. Chem.* **29**, 3093 (1964); Tolgyesi, *Can. J. Chem.* **43**, 343 (1965); and Olah and Overchuk, *Can. J. Chem.* **43**, 3279 (1965).

[16] Olah, Kuhn, Flood, and Hardie, *J. Am. Chem. Soc.* **86**, 1039, 1044 (1964).

[17] See Christen and Zollinger, *Helv. Chim. Acta* **45**, 2057, 2066 (1962); Christen, Koch, Simon, and Zollinger, *Helv. Chim. Acta* **45**, 2077 (1962); Brown, *J. Chem. Soc.* **1959**, 2224, 2232; Gold, Lambert, and Satchell, *J. Chem. Soc.* **1960**, 2461. For a contrary view, see Kresge and Chiang, *J. Am. Chem. Soc.* **83**, 2877 (1961).

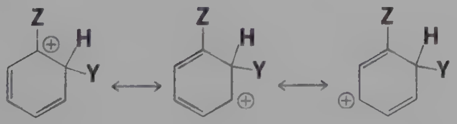
[18] For a review, see Ferguson, *Chem. Rev.* **50**, 47–67 (1952).

zene gave 93% m-dinitrobenzene, 6% of the ortho, and 1% of the para isomer.

The orientation and reactivity effects of each group are explained on the basis of inductive and resonance effects on the stability of the intermediate σ-complex. In order to understand why we may use this approach, it is necessary to know that in these reactions the product is usually kinetically and not thermodynamically controlled (see p. 204). Some of the reactions are irreversible and the others are usually stopped well before equilibrium is reached. Therefore, which of the three possible intermediates is formed is dependent not on the thermodynamic stability of the products, but on the activation energy necessary to form each of the three intermediates. It is not easy to predict which of the three activation energies is lowest, but we may make the assumption that the transition state (the top of the hump) resembles the intermediate more than it does the starting materials; that is, that anything which will increase the stability of the *intermediate* will also lower the activation energy necessary to attain it. Since the intermediate, once formed, is rapidly converted to products, we may use the relative stabilities of the three intermediates as guides to predict which products will predominantly form. Of course, if reversible reactions are allowed to proceed to equilibrium, we may get product ratios which are quite different. For example, the sulfonation of naphthalene at 80°, where the reaction does not reach equilibrium, gives mostly α-naphthalenesulfonic acid,[19] while at 160°, where equilibrium is obtained, the β-isomer predominates.[20] An example from the benzene series is as follows: when ethylbenzene is ethylated under the usual Friedel-Crafts conditions (reaction **1-12**), the products are chiefly the o- and p-diethylbenzenes, but treatment of either o-, m-, or p-diethylbenzene with $AlCl_3$ eventually gives an equilibrium mixture which contains 3% o-, 69% m-, and 28% p-diethylbenzenes.[21] This result is in accord with the thermodynamic stabilities of the products.[22]

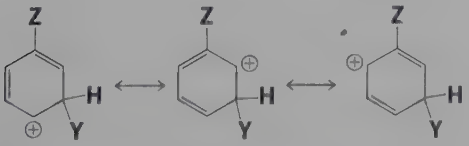
Now that we see why we may use the relative stabilities of the σ-complexes to predict orientation effects, let us examine the three possible complexes:

Ortho



9

Meta



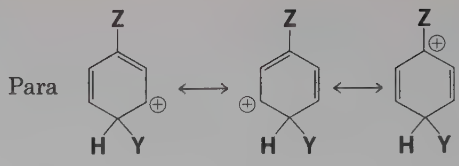
---

[19] Fierz and Weissenbach, *Helv. Chim. Acta* **3,** 312 (1920).

[20] Witt, *Ber.* **48,** 743 (1915).

[21] Olah, Meyer, and Overchuk, *J. Org. Chem.* **29,** 2313 (1964).

[22] Stull, in Olah, "Friedel-Crafts and Related Reactions," vol. 1, pp. 980–982, Interscience Publishers, Inc., New York, 1963. Actually the values in this reference are for the three xylenes, but the order of stability is undoubtedly the same for the diethylbenzenes.

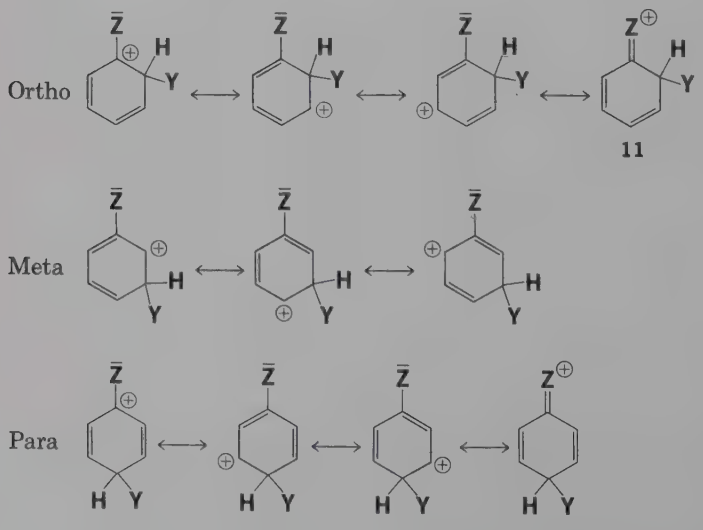


10

For each complex we see that the ring has a positive charge. We may therefore predict that any group Z which has an electron-donating inductive effect should stabilize all three complexes (relative to **1**), but that electron-withdrawing groups, which increase the positive charge on the ring, should destabilize them. But we may make a further prediction concerning inductive effects. These taper off with distance and are thus strongest at the carbon connected to the group Z. But of the three complexes, only the ortho and para have any positive charge at this carbon. None of the resonance forms of the meta complex has a positive charge there, and so the hybrid has none either. Therefore, $+I$ groups should stabilize all three complexes, but mostly the ortho and para, so they should be not only activating, but ortho-para-directing as well. On the other hand, $-I$ groups, by removing electron density, should destabilize all three complexes, but mostly the ortho and para, and should be not only deactivating, but also meta-directing.

These conclusions are correct as far as they go, but they do not lead to the proper results in all cases. In many cases there is *resonance interaction* between Z and the ring, and this also affects the relative stability, in some cases in the same direction as the I effect, but in others differently.

Some Z groups have a pair of electrons (usually unshared) which may be contributed *toward* the ring. The three complexes would then look like this:



11

12

For each complex the same three canonical forms may be drawn as before, but now we may draw an extra form for the ortho and the para complexes. The stability of these two is increased by the extra form not only because it is another canonical form, but because it is more stable than the others and makes a greater contribution to the hybrid. Every atom (except, of course, hydrogen) in these forms (**11** and **12**) has a complete octet, while all the other forms have one carbon atom with a sextet. No corresponding form may be drawn for the meta isomer. The inclusion of this form in the hybrid lowers the energy not only because of rule 6 (p. 35), but also because it spreads the positive charge over a larger area—out onto the group Z. Groups with a pair of electrons to contribute would be expected then, in the absence of *I* effects, not only to direct ortho and para, but also to activate the reaction for these positions.

On the basis of these discussions, we may distinguish three types of groups.

1. Groups which contain an unshared pair on the atom connected to the ring. In this category are O^-, NR_2, NHR, NH_2,[23] OH, OR, NHCOR, OCOR, NO, SR, and the four halogens. The SH group would probably belong here too except that in the case of thiophenols, electrophiles usually attack the sulfur rather than the ring, and ring substitution is not feasible with these substrates.[24] The resonance explanation predicts that all of these groups should be ortho-para-directing, and they are, although all except O^- are inductive-withdrawing (p. 21). Therefore, for these groups, resonance is more important than the inductive effect. This is especially true for NR_2, NHR, NH_2, and OH, which are *strongly* activating, as is O^-. The other groups are mildly activating, except for the halogens, which are deactivating. Fluorine is the least deactivating, and fluorobenzenes usually show a reactivity approximating that of benzene itself. The other three halogens deactivate about equally. In order to explain why chlorine, bromine, and iodine deactivate the ring even though they direct ortho-para, we must assume that the canonical forms **11** and **12** make such great contributions to the respective hybrids that they make the ortho and para complexes more stable than the meta even though the $-I$ effect of the halogen is withdrawing sufficient electron density from the ring to deactivate it. The three halogens make the ortho and para complexes more stable than the meta, but less stable than the unsubstituted **1**. For the other groups which contain an unshared pair, the ortho and para complexes are more stable than either the meta or the unsubstituted complex. For most of the groups in this category, the meta complex is more stable than **1**, so that groups such as NH_2, OH,

---

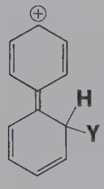
[23] It must be remembered that in acid solution amines are converted to their conjugate acids, which for the most part are meta-directing (type 2). Therefore in acid (which is the most common medium for electrophilic substitutions) amino groups may direct meta. However, unless the solution is highly acidic, there will be a small amount of free amine present, and since amino groups are activating and the conjugate acids deactivating, ortho-para direction is often found even under acidic conditions.

[24] Tarbell and Herz, *J. Am. Chem. Soc.* **75**, 4657 (1953). Ring substitution *is* possible if the SH group is protected. For a method of doing this, see Walker and Lieb, *J. Org. Chem.* **27**, 4455 (1962); and Walker, *J. Org. Chem.* **31**, 835 (1966).

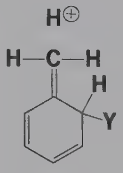
etc., activate the meta positions too, but not so much as the ortho and para positions (see also the discussion on pp. 391–393).

2. Groups which lack an unshared pair on the atom connected to the ring and which are $-I$. In this category we may list, in approximate order of decreasing deactivating ability, NR_3^+, NO_2, CN,[25] SO_3H, CHO, COR, COOH, COOR, $CONH_2$, CCl_3, and NH_3^+. Also in this category are all other groups with a positive charge on the atom directly connected to the ring (for example, SR_2^+, PR_3^+, etc.), and many groups with positive charges on atoms farther away, since often these are still powerful $-I$ groups. The inductive-effect explanation predicts that these should all be meta-directing and deactivating, and this is the case.[26] This is especially true for groups with a positive charge on the atom directly connected to the ring (this includes nitro), since for these, canonical forms **9** and **10** have two positive charges on adjacent atoms, which destabilize the ortho and para complexes even more than otherwise.

3. Groups which lack an unshared pair on the atom connected to the ring and which are ortho-para-directing. In this category are alkyl groups, aryl groups, and the COO^- group,[27] all of which activate the ring. We shall discuss them separately. Since aryl groups are $-I$ groups, they might seem to belong to category 2. They are nevertheless ortho-para-directing and activating. This can be explained in a similar manner as in category 1, with a pair of electrons from the aromatic sextet playing the part played by the unshared pair, so that we have forms like **13**. The effect of negatively charged groups like COO^- is easily explained by the I effect, since there is no resonance interaction between the group and the ring. The effect of alkyl groups may be explained in the same way, but in addition, we may also draw resonance forms even though there is no unshared pair. These, of course, are hyperconjugation forms like **14**. This effect, like the inductive effect, predicts activation and ortho-para direction, so that it is not possible to say how much each effect is contributing to the result. In activating ability, alkyl groups usually follow the Baker-Nathan order (p. 57), but not always.[28]



13



14

---

[25] When the cyano group is complexed to iron (C≡N→Fe), it is ortho-para-directing and activating: Heldt, *J. Org. Chem.* **27**, 2604 (1962).

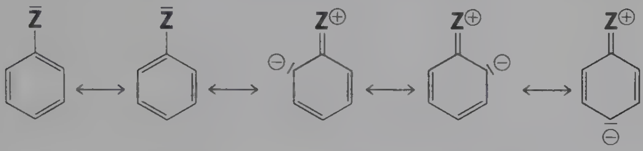
[26] The NH_3^+ group directs para about as much as it directs meta (Brickman and Ridd, *J. Chem. Soc.* **1965**, 6845). However, the NH_2Me^+, $NHMe_2^+$, and NMe_3^+ groups give more meta than para substitution (Brickman, Utley, and Ridd, *J. Chem. Soc.* **1965**, 6851). The percentage of para substitution decreases with the increasing number of methyl groups.

[27] Spryskov and Golubkin, *J. Gen. Chem. USSR* **31**, 833 (1961). Since this group is present only in alkaline solution, where electrophilic substitution is not often done, it is seldom met with.

[28] Eaborn and Taylor, *J. Chem. Soc.* **1961**, 247; Stock, *J. Org. Chem.* **26**, 4120 (1961).

The cyclopropyl group is highly activating, since cyclopropylbenzene could be brominated at −75° and nitrated at −50°.[29]

Up to now, in this section, we have explained orientation and reactivity on the basis of stability of the σ-complex. In the past, the facts were generally explained on the basis of electron distribution in the starting molecule. The theory behind this was that an electrophile will attack those positions at which the electron density is greatest. For example, we may draw these canonical forms for groups with an unshared pair (and the phenyl group):



The ortho and para positions are more electron-rich than the meta positions because of the contributions from the dipolar forms. Thus, all such groups are ortho-para-directing. In most cases this approach predicts the correct results, but it is less successful than the other. For example, it cannot explain why groups like NR_3^+, CCl_3, etc., are meta-directing and why COO^- is ortho-para-directing. Since there is no resonance interaction between these groups and the ring, only the inductive effect is operating. This effect, in the starting compound, is sufficient to explain why NR_3^+, CCl_3, etc., are deactivating and why COO^- is activating. But the inductive effect is supposed to weaken with distance, and if that were so, NR_3^+ should be para-directing, since the deactivating effect would be least there, and COO^- should favor ortho and meta, but not para. Another experimental result not in accord with this approach is observed in electrophilic and nucleophilic substitution on pyridine-N-oxide. If an electrophile attacks at positions of highest electron density, a nucleophile would certainly not be expected to attack the same positions. Yet both electrophilic and nucleophilic attacks on pyridine-N-oxide occur at the 2- and 4-positions.[30]

The Ortho-Para Ratio.[31] When an ortho-para-directing group is on a ring, it is usually difficult to predict how much of the product will be the ortho isomer and how much the para isomer. Indeed, these proportions may depend greatly upon the reaction conditions. For example, chlorination of toluene gives anywhere from 62% *o*-chlorotoluene and 38% of the para isomer to 34% of the ortho and 66% of the para compound.[32] Nevertheless, certain points can be made. On a purely statistical basis there would be 67% ortho and 33% para, since there are two ortho positions and only one para. However, if either the group on the ring or the attacking group is large, then steric hindrance inhibits formation of the ortho product and thus increases the amount of the para isomer. An example of this may be seen in the nitration, under the same conditions, of toluene and *tert*-butylbenzene. The former gave 58% of the ortho compound and 37% of the para, while the more bulky *tert*-butyl group gave 16% of the ortho and 73% of the para product.[33] A few groups are so large that they give almost entirely para direction.

---

[29] Levina and Gembitskii, *J. Gen. Chem. USSR* **31**, 3242 (1961).

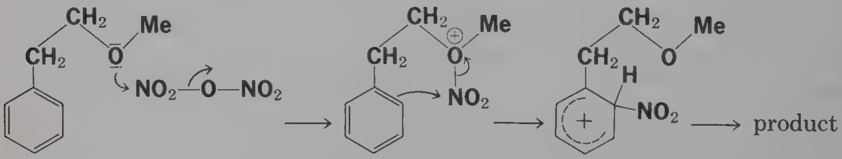
[30] Jaffé, *J. Am. Chem. Soc.* **76**, 3527 (1954). This is a useful way of putting groups into the 4-position of pyridine, since pyridine itself, under the acid conditions normally used in electrophilic substitution, where it is the conjugate acid which is actually attacked, directs to the 3-position.

[31] For a discussion, see Norman and Taylor, Ref. 1, pp. 301–310.

[32] Stock and Himoe, *J. Am. Chem. Soc.* **83**, 4605 (1961).

When the ortho-para-directing group is one with an unshared pair (this, of course, applies to most of them), there is another effect which increases the amount of para product at the expense of the ortho. A comparison of the intermediates involved (p. 384) shows that **11** is a canonical form with an ortho-quinonoid structure, while **12** has a para-quinonoid structure. Since we know that *para*-quinones are more stable than the ortho isomers, it seems reasonable to assume that **12** is more stable than **11** and therefore contributes more to the hybrid and increases its stability in comparison with the ortho intermediate.

In some cases a high ortho-para ratio is observed because of interaction between the electrophile and the directing group. For example, methyl phenethyl ether gives a higher ortho-para ratio when nitrated with N_2O_5 than it does with the more usual mixture of nitric and sulfuric acids, where the attacking entity is NO_2^+ (reaction **1-2**). This behavior has been ascribed to the following mechanism:[34]



One final point can be made: with groups where the inductive effect is important, we should look for a greater effect at the ortho position than at the para, since inductive effects decrease with distance. Fluorine, which has the strongest $-I$ effect of the four halogens, should therefore have a greater relative deactivating effect at the ortho position compared to the para than chlorine has, and the effect of chlorine should be greater than that of bromine, etc. Consequently, in electrophilic substitution on the halobenzenes, iodobenzene should give the highest amount of ortho product and fluorobenzene the smallest. Nitration of the halobenzenes gave ortho products as follows: PhF, 12%; PhCl, 30%; PhBr, 38%; PhI, 41%.[35]

Orientation in Benzene Rings with More than One Substituent.[36] It is often possible in these cases to predict the correct isomer. In many cases the groups already on the ring reinforce each other. Thus, 1,3-dimethylbenzene is substituted at the 4-position, since this is ortho to one group and para to the other, but not at the 5-position, which is meta to both. Likewise the incoming group in *p*-chlorobenzoic acid goes to the position ortho to the chloro and meta to the carboxyl group.

---

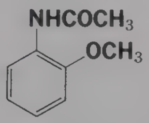
[33] Nelson and Brown, *J. Am. Chem. Soc.* **73**, 5605 (1951).

[34] Norman and Radda, *Proc. Chem. Soc.* **1960**, 423; *J. Chem. Soc.* **1961**, 3030.

[35] Holleman, *Chem. Rev.* **1**, 218 (1925).

[36] For a quantitative discussion, see pp. 391–393.

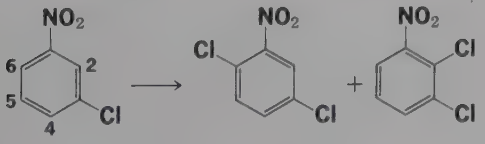
When the groups oppose each other, predictions may be more difficult. In a case such as **15**, where two groups of about equal directing ability are in competing positions, all four products may be expected, and it is not easy to predict the proportions, except that steric hindrance should probably reduce the yield of substitution ortho to the acetamido group, especially for large electrophiles. It is, of course, possible to make predictions on the basis of inductive and resonance effects, etc., but only a rash person would expect to get close to the experimental values every time. Mixtures of about equal proportions are frequent in such cases. Results are often hard to explain. For example, acetylation of *ortho*-bromofluorobenzene gives mostly 4-acetyl-2-bromofluorobenzene, that is, the fluoro group controls the direction; but with *para*-bromofluorobenzene, the product is 3-acetyl-4-bromofluorobenzene, that is, the bromo group controls.[37]



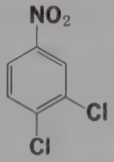
15

Nevertheless, even when groups on a ring oppose each other, there are some regularities.

1. If a strongly activating group competes with a weaker one or with a deactivating group, the former controls. Thus *o*-cresol gives substitution mainly ortho and para to the *hydroxy* group and not the methyl. For this purpose we may arrange the groups thusly: NH_2, OH, NR_2, $O^- >$ OR, OCOR, NHCOR $>$ R, Ar $>$ halogen $>$ meta-directing groups.
2. All other things being equal, a third group is least likely to enter between two groups in the meta relationship. This effect is the result of steric hindrance and increases in importance with the size of the groups on the ring and with the size of the attacking species.
3. When a meta-directing group is meta to an ortho-para-directing group, the incoming group primarily goes ortho to the meta-directing group, rather than para. For example, chlorination of **16** gives mostly **17**. The importance of this effect is underscored by the fact that **18**, which is in violation



16 **17** **18**



19

---

[37] Quang, Diêp, and Buu-Hoï, *Rec. trav. chim.* **83**, 1142 (1964).

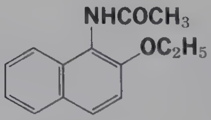
of the preceding rule, is formed in smaller amounts, but **19** is not formed at all. This is called the *ortho effect,*[38] and many such examples are known. Another is the nitration of *p*-bromotoluene, which gives 2,3-dinitro-4-bromotoluene. In this case, once the first nitro group came in, the second was directed ortho to it, rather than para, even though this meant that the group had to come in between two groups in the meta position. There is no good explanation yet for the ortho effect, although possibly there is intramolecular assistance from the meta-directing group.

It is interesting that chlorination of **16** illustrates all three rules. Of the four positions open to the electrophile, the 5-position violates rule 1, the 2-position rule 2, and the 4-position rule 3. The principal attack is therefore at position 6.

Orientation in Other Ring Systems.[39] In fused ring systems the positions are not equivalent, and there is usually a preferred orientation even in the unsubstituted hydrocarbon. The preferred positions may often be predicted as for benzene rings. Thus it is possible to draw more canonical forms for the σ-complex when naphthalene is attacked at the 1-position than when it is attacked at the 2-position, and the 1-position is the preferred site of attack,[40] though, as previously mentioned (p. 383), the isomer formed by substitution at the 2-position is thermodynamically more stable and is the product if the reaction is reversible and equilibrium is reached. Naphthalene is activating compared to benzene, and substitution is faster at both positions.

Heterocyclic compounds, too, have nonequivalent positions, and the principles are similar. Furan, thiophene, and pyrrole are chiefly substituted in the 2-position, and all are substituted faster than benzene. For pyridine it is not the free base which is attacked, but the conjugate acid, pyridinium ion.[41] The 3-position is most reactive, but the reactivity in this case is much less than that of benzene, being similar to that of nitrobenzene.

When fused ring systems are substituted, predictions are frequently hard to make. For example, chlorination or nitration of **20** gives mainly the 4-derivative, but bromination yields chiefly the 6-compound.[42]



20

---

[38] For a review, see Hammond and Hawthorne, in Newman, "Steric Effects in Organic Chemistry," pp. 164–200, 178–182, John Wiley & Sons, Inc., New York, 1956.

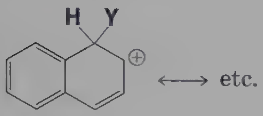
[39] For a review of substitution on nonbenzenoid aromatic systems, see Hafner and Moritz, in Olah, "Friedel-Crafts and Related Reactions," vol. IV, pp. 127–183, Interscience Publishers, Inc., New York, 1965.

[40] For a discussion of the preferred site of attack for many ring systems, see de la Mare and Ridd, Ref. 1, pp. 169–209.

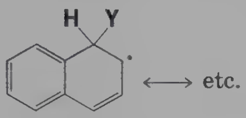
[41] Olah, Olah, and Overchuk, *J. Org. Chem.* **30**, 3373 (1965).

[42] Bell, *J. Chem. Soc.* **1959**, 519.

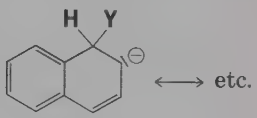
In alternant hydrocarbons (p. 46) the reactivity at a given position is proportional to its free valence (p. 55), not only for electrophilic substitution, but also for nucleophilic and free-radical substitution, because the same kind of resonance can be shown in all three types of intermediate (compare **21**, **22**, and **23**). Attack at the position which will best delocalize a positive charge will also best delocalize a negative charge or an unpaired electron. Since free valence is a measure of the ability of the system to spread the charge in the intermediate, it is proportional to the reactivity.[43] Most results are in accord with these predictions. For example, naphthalene is attacked primarily at the 1-position by NO_2^+, NH_2^-, and Ph·, and always more readily than benzene.



21



22



23

Quantitative Treatments of Reactivity in the Substrate. Quantitative rate studies of aromatic substitutions are complicated by the fact that there are usually several hydrogens which can leave, so that measurements of overall rate ratios do not give a complete picture as they do in nucleophilic substitutions, where it is easy to compare substrates which have only one possible leaving group in a molecule. What is needed is not, say, the overall rate ratio for acetylation of toluene versus that for benzene, but the *rate ratio at each position*. These can be calculated from the overall rates and a careful determination of the proportion of isomers formed. We may thus define the *partial rate factor* for a given group and a given reaction as the rate of substitution at a single position relative to a single position in benzene. For example, for acetylation of toluene the partial rate factors are: for the ortho position $o_f^{\text{Me}} = 4.5$; for the meta $m_f^{\text{Me}} = 4.8$; and for the para $p_f^{\text{Me}} = 749$.[44] This means that toluene is acetylated at the ortho position 4.5 times as fast as is a single position in benzene, or 0.75 times as fast as the overall rate of acetylation of benzene. A partial rate factor greater than 1 for a given position indicates that the group in question is activating that position for the given reaction. Partial rate factors differ from one reaction to another and are even different, though less so, for the same reaction under different conditions.

Once we know the partial rate factors, we may predict the proportions of isomers to be obtained when two or more groups are present on a ring. For example, if the two methyl groups in *m*-xylene have the same effect as the methyl group in toluene, we may calculate the theoretical partial rate fac-

---

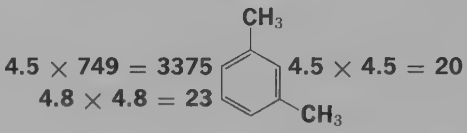
[43] There are some exceptions. In biphenylene (p. 50) the highest free valence is at the 1-position, but substitution occurs at the 2-position [Pullman and Pullman, *Progr. Org. Chem.* **4**, 50 (1958)].

[44] Brown, Marino, and Stock, *J. Am. Chem. Soc.* **81**, 3310 (1959).

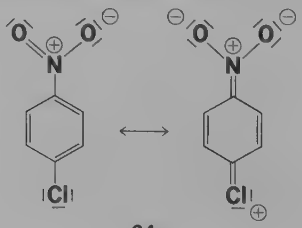
TABLE 2. Calculated and experimental isomer distributions in the acetylation of *m*-xylene[45]

	Isomer distribution, %	
Position	*Calculated*	*Observed*
2	0.30	0
4	99.36	97.5
5	0.34	2.5

tors at each position by multiplying those from toluene, so that they should be as indicated:



From this it is possible to calculate the overall theoretical rate ratio for acetylation of *m*-xylene relative to benzene, since this is one-sixth of the sum of the partial rate factors (in this case 1130), and the isomer distribution if the reaction is kinetically controlled. The overall rate ratio actually is 347,[45] and the calculated and observed isomer distributions are listed in Table 2. In this case, and in many others, agreement is fairly good, but this is not always true. For example, the treatment predicts that for 1,2,3-trimethylbenzene, there should be 35% 5-substitution and 65% 4-substitution, but acetylation gave 79% 5-substitution and 21% of the 4-isomer. The treatment is thrown off by steric effects, such as those mentioned earlier (p. 389), and by resonance interaction *between* groups (for example, **24**), which must make the results deviate from simple additivity of the effects of the groups.



24

Another approach which avoids the problem created by having competing leaving groups present in the same substrate is the use of substrates which contain only one leaving group. This is most easily accomplished by use of a leaving group other than hydrogen. By this means overall rate ratios may be measured for specific positions. Table 3 contains the results of two such studies. The results are in good agreement with each other and give a reac-

---

[45] Marino and Brown, *J. Am. Chem. Soc.* **81**, 5929 (1959).

TABLE 3. Relative rates for two reactions with leaving groups other than hydrogen
Reaction *a* is cleavage of $ArSiMe_3$ in H_2SO_4-HOAc-H_2O at 50.18°.[46] Reaction *b* is cleavage of $ArGePh_3$ by aqueous $HClO_4$-MeOH[47]

	Relative rates	
Group	*Reaction a*[46]	*Reaction b*[47]
p-NO_2	1.22×10^{-4}	
p-NMe_3^+	3.84×10^{-4}	
p-COOH	1.48×10^{-3}	
m-Cl	0.012	0.0165
p-Br	0.104	0.13
p-I	0.101	0.131
p-Cl	0.190	0.167
m-Ph	0.33	
m-OMe	0.38	0.58
p-F	0.95	0.9
H	1	1
m-Me		2.1
p-Ph	2.83	2.69
o-Ph	5.85	3.22
o-Me		12.4
p-Me	18.0	14.1
o-OMe		207
p-OMe	1010	540
p-OH		2730
p-NMe_2		3×10^6

tivity order quite consistent with that given before for hydrogen as leaving group.

A Quantitative Treatment of Reactivity of the Electrophile. The Selectivity Relationship. Not all electrophiles are equally powerful. The nitronium ion attacks not only benzene, but also aromatic rings which contain a strongly deactivating group. On the other hand, diazonium ions couple only with rings containing a powerful activating group. Attempts have been made to correlate the influence of substituents with the power of the attacking group. The most obvious way to do this is with the Hammett equation (p. 239):

$$\log \frac{k}{k_0} = \rho\sigma$$

For aromatic substitution, k_0 is divided by 6, and for meta substitution, k is divided by 2, so that comparisons are made for only one position. It was

---

[46] Deans and Eaborn, *J. Chem. Soc.* **1959,** 2299.
[47] Eaborn and Pande, *J. Chem. Soc.* **1961,** 297.

TABLE 4. Relative rates and product distributions in some electrophilic substitutions on toluene and benzene[49]

Reaction	Relative rate $k_{\text{toluene}}/k_{\text{benzene}}$	Product distribution, % m	p
Bromination	605	0.3	66.8
Chlorination	350	0.5	39.7
Benzoylation	110	1.5	89.3
Nitration	23	2.8	33.9
Mercuration	7.9	9.5	69.5
Isopropylation	1.8	25.9	46.2

soon found that, while this approach worked fairly well for electron-withdrawing groups, it failed for those which are electron-donating. However, by the use of σ^+ instead of σ, since a positive charge develops during the transition state, more satisfactory correlations could be made even for electron-donating groups (see p. 241 for a list of σ^+ values). The ρ values correspond to the reactivity of the electrophile and vary not only with the electrophile, but also with conditions. Of course, this approach is completely useless for ortho substitution, since the Hammett equation does not apply to them.

A modification of the Hammett approach, suggested by Brown, is called the *selectivity relationship*,[48] and is based on the fact that reactivity of a species varies inversely with selectivity. Table 4 shows how electrophiles may be arranged in order of selectivity as measured by two indexes: (1) how selective they are in attacking toluene rather than benzene and (2) their selectivity between the meta and para positions in toluene.[49] As the table shows, an electrophile more selective in one respect is also more selective in the other. In many cases, electrophiles which are known to be more stable and hence less reactive than others show a higher selectivity, as would be expected. For example, the *tert*-butyl cation is more stable than the isopropyl (p. 126) and more selective, and Br_2 is more selective than Br^+. However, deviations from the relationship are known. Selectivity depends not only on the nature of the electrophile, but also on the temperature. As expected, it normally decreases with increasing temperature.

Brown assumed that a good measurement of selectivity was the ratio of the para and meta partial rate factors, and he defined the selectivity S_f of a reaction as

$$S_f = \log \frac{p_f}{m_f}$$

---

[48] For a comprehensive review, see Stock and Brown, *Advan. Phys. Org. Chem.* **1,** 35–154 (1963). Shorter reviews are by Olah, in Olah, "Friedel-Crafts and Related Reactions," vol. 1, pp. 905–927, Interscience Publishers, Inc., New York, 1963, and by Brown and Stock, *J. Am. Chem. Soc.* **84,** 3298 (1962).

[49] Stock and Brown, Ref. 48, p. 45.

TABLE 5. Values of m_f, p_f, S_f, and ρ for three reactions of toluene[50]

Reaction	m_f	p_f	S_f	ρ
$\text{PhMe} + \text{EtBr} \xrightarrow[\text{benzene, 25°}]{\text{GaBr}_3}$	1.56	6.02	0.587	−2.66
$\text{PhMe} + \text{HNO}_3 \xrightarrow[\text{45°}]{\text{90\% HOAc}}$	2.5	58	1.366	−6.04
$\text{PhMe} + \text{Br}_2 \xrightarrow[\text{25°}]{\text{85\% HOAc}}$	5.5	2420	2.644	−11.40

That is, the more reactive an attacking species, the less preference it has for the para position as against the meta (of course this assumes that an ortho-para-directing group is present). Combining the modified Hammett $\sigma^+\rho$ relationship with the linearity between log S_f and log p_f and between log S_f and log m_f, it is possible to derive the following expressions:

$$\log p_f = \frac{\sigma_p{}^+}{\sigma_p{}^+ + \sigma_m{}^+} \log \frac{p_f}{m_f}$$

$$\log m_f = \frac{\sigma_m{}^+}{\sigma_p{}^+ + \sigma_m{}^+} \log \frac{p_f}{m_f}$$

From these equations, $\sigma_p{}^+$ and $\sigma_m{}^+$, and hence ρ values, can be calculated. Examples of values for some reactions are given in Table 5. This type of treatment works well with groups which are not very polarizable, such as methyl. For more polarizable groups the correlations are sometimes satisfactory, and sometimes not, probably because each electrophile, in the transition state, makes a different demand on the electrons of the substituent group. Not only are there substrates for which the treatment is poor, but it also fails with very powerful electrophiles, where π-complex formation is rate-determining (p. 382). In such cases the *position* of attack is not determined in the slow step, so that the p/m ratio is not related to the rate of the reaction. More complex treatments have been devised.[51]

REACTIONS

The reactions in this chapter are classified according to leaving group, with hydrogen replacements being treated first; then rearrangements in which the attacking entity is first cleaved from another part of the molecule (hydrogen is also the leaving group in these cases); and finally replacements of other leaving groups.

---

[50] Stock and Brown, *J. Am. Chem. Soc.* **81,** 3323 (1959). Stock and Brown, Ref. 48, present many tables of these kinds of data.

[51] For example, see Yukawa and Tsuno, *Bull. Chem. Soc. Japan* **32,** 971 (1959); Knowles, Norman, and Radda, *J. Chem. Soc.* **1960,** 4885; Norman and Radda, *Tetrahedron Letters* **1962,** 125.

Hydrogen as the Leaving Group in Simple Substitution Reactions

A. Hydrogen as the electrophile

1-1 Hydrogen exchange

$$\mathrm{ArH} + \mathrm{D}^+ \rightleftharpoons \mathrm{ArD} + \mathrm{H}^+$$

The hydrogen exchange reaction is used chiefly to study mechanistic questions,[52] but can also be useful to deuterate or tritiate aromatic rings selectively.[53] The usual directive effects apply, and, for example, phenol, treated with D_2O, gives slow exchange on heating, with only ortho and para hydrogens being exchanged.[54] Strong acids, of course, exchange faster, and this exchange must be taken into account when studying the mechanism of any aromatic substitution catalyzed by acids. Hydrogen exchange may also be effected with strong bases, such as NH_2^-. In these cases the slow step is the proton transfer:

$$\mathrm{ArH} + \mathrm{B} \longrightarrow \mathrm{Ar}^- + \mathrm{BH}^+$$

so that the S_E1 mechanism and not the usual σ-complex mechanism is operating.[55] As would be expected from the S_E1 mechanism, only inductive and not resonance effects of substituents affect the rates.[56]

B. Nitrogen electrophiles

1-2 Nitration

$$\mathrm{ArH} + \mathrm{HNO_3} \xrightarrow{\mathrm{H_2SO_4}} \mathrm{ArNO_2}$$

Most aromatic compounds can be nitrated, and the reaction has been carried out with a variety of nitrating agents.[57] The most common reagent is a mixture of concentrated nitric and concentrated sulfuric acids, but, especially with active substrates, the reaction can be carried out with nitric acid alone, or in water, acetic acid, or acetic anhydride. If anhydrous conditions are required, nitration may be effected with N_2O_5 in CCl_4, in the presence of P_2O_5, which removes the water formed in the reaction. Nitration in alkaline media can be accomplished with esters of nitric acid, such as ethyl nitrate ($EtONO_2$). These reagents may also be used with proton or Lewis acid catalysts. Other nitrating agents are mixed anhydrides such as acetyl nitrate, CH_3COONO_2 (see reaction **0-33**, p. 327, for their preparation), nitryl halides with a Friedel-Crafts catalyst such as $FeCl_3$,[58] and nitronium salts, such as NO_2^+ BF_4^- and NO_2^+ PF_6^-.[59] With active substrates such as amines and phenols, nitration may be accomplished by nitrosation under oxidizing conditions, with a mixture of dilute nitrous and nitric acids, so that what is actually happening is nitrosation (reaction **1-3**) followed by oxidation:

---

[52] For example, see Melander, *Arkiv Kemi* **17**, 291 (1961), **18**, 195 (1961); Eaborn and Taylor, *J. Chem. Soc.* **1960**, 3301; Melander, in "The Transition State," *Chem. Soc.* (*London*) Spec. Publ. 16, pp. 77–90 (1962).

[53] For a review of aromatic hydrogen exchange, see Norman and Taylor, Ref. 1, pp. 202–224.

[54] Small and Wolfenden, *J. Chem. Soc.* **1936**, 1811.

[55] Shatenshtein, *Tetrahedron* **18**, 95 (1962).

[56] Hall, Libby, and James, *J. Org. Chem.* **28**, 311 (1963).

[57] For reviews, see de la Mare and Ridd, Ref. 1, pp. 48–93; Norman and Taylor, Ref. 1, pp. 61–91, 313–315; Gillespie and Millen, *Quart. Rev.* (*London*) **2**, 277–306 (1948); Schofield, *Quart. Rev.* (*London*) **4**, 382–403 (1950); and Olah and Kuhn, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 1393–1491, Interscience Publishers, Inc., New York, 1964.

$$\mathrm{ArH} + \mathrm{HONO} \longrightarrow \mathrm{ArNO} + \mathrm{HNO_3} \longrightarrow \mathrm{ArNO_2}$$

When amines are nitrated under strong acid conditions, meta orientation is generally observed, since the species undergoing nitration is actually the conjugate acid of the amine. If the conditions are less acidic, the free amine is nitrated, and the orientation is ortho-para. Although the free base may be present in much smaller amounts than the conjugate acid, it is far more susceptible to aromatic substitution.

Since the nitro group is deactivating, it is usually easy to stop the reaction after one group has entered the ring, but a second and a third group may be introduced if desired, especially when an activating group is also present. Even *m*-dinitrobenzene itself can be nitrated if vigorous conditions are applied. This has been accomplished with anhydrous nitric and fuming sulfuric acids at 110°.[60]

With most of the reagents mentioned (except for oxidative nitrosation) the attacking species is the nitronium ion NO_2^+. Among the ways in which this ion is formed are the following:

1. In concentrated sulfuric acid, by an acid-base reaction in which nitric acid is the base:

$$\mathrm{HNO_3} + 2\mathrm{H_2SO_4} \rightleftharpoons \mathrm{NO_2^+} + \mathrm{H_3O^+} + 2\mathrm{HSO_4^-}$$

This ionization is essentially complete.

2. In concentrated nitric acid alone, by a similar acid-base reaction in which one molecule of nitric acid is the acid and another the base:

$$2\mathrm{HNO_3} \rightleftharpoons \mathrm{NO_2^+} + \mathrm{NO_3^-} + \mathrm{H_2O}$$

This equilibrium lies to the left (about 4% ionization), but enough NO_2^+ is formed for nitration to occur.

3. The equilibrium just mentioned occurs to a small extent even in organic solvents.

4. In N_2O_5 there is spontaneous dissociation:

$$\mathrm{N_2O_5} \rightleftharpoons \mathrm{NO_2^+} + \mathrm{NO_3^-}$$

---

[58] Kuhn and Olah, *J. Am. Chem. Soc.* **83**, 4564 (1961).

[59] Olah and Kuhn, *J. Am. Chem. Soc.* **84**, 3684 (1962).

[60] Radcliffe and Pollitt, *J. Soc. Chem. Ind. (London)* **40**, 45T (1921).

5. When nitronium salts are used, NO_2^+ is, of course, present to begin with. However, there is evidence that in some solvents, such as tetramethylene sulfone, it is the ion pair which actually attacks the ring.[61] Esters, anhydrides, and acyl halides of nitric acid all ionize to form NO_2^+.

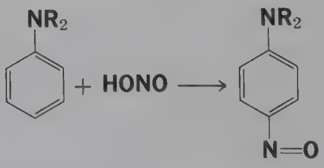
There is a great deal of evidence for the fact that the nitronium ion is present in most nitrations and that it is the attacking entity.[62] Some of this evidence is as follows:

1. Nitric acid has a peak in the Raman spectrum. When nitric acid is dissolved in concentrated sulfuric acid, the peak disappears, and two new peaks appear, one at 1400 cm^{-1} attributable to NO_2^+, and one at 1050 cm^{-1} due to HSO_4^-.[63]
2. Upon addition of nitric acid, the freezing point of sulfuric acid is lowered about four times the amount expected if no ionization took place.[64] This means that the addition of one molecule of nitric acid results in the production of four particles, which is strong evidence for the ionization reaction given on page 397, between nitric and sulfuric acids.
3. The fact that nitronium salts, in which nitronium ion is known to be present (by x-ray studies), nitrate aromatic compounds shows that this ion does attack the ring.
4. The rate of the reaction, with most reagents, is proportional to the concentration of NO_2^+, and not to that of other species. When the reagent produces this ion in small amounts, the attack is slow, and only active substrates can be nitrated.

In a few cases (mostly when organic solvents are used) the attacking entity is not nitronium ion, but a species such as $NO_2\text{-}OH_2^+$ or $NO_2\text{-}OAcH^+$. It is obvious that in species like these another molecule (in these cases water and acetic acid, respectively) is acting as a "carrier" of nitronium ions. In such cases the mechanism is essentially the same, but the carrier drops off somewhere in the process (p. 377).

OS **I,** 372, 396, 408; **II,** 254, 434, 438, 447, 449, 459, 466; **III,** 337, 644, 653, 658, 661, 837; **IV,** 42, 364, 654, 711, 722, 735; **40,** 96; **42,** 95; **44,** 34; **46,** 85.

1-3 Nitrosation



---

[61] Olah, Kuhn, Flood, and Evans, *J. Am. Chem. Soc.* **84**, 3687 (1962).

[62] For an exhaustive study of this reaction, see Hughes, Ingold, and coworkers, *J. Chem. Soc.* **1950**, 2400–2684.

[63] Ingold, Millen, and Poole, *J. Chem. Soc.* **1950**, 2576.

[64] Gillespie, Graham, Hughes, Ingold, and Peeling, *J. Chem. Soc.* **1950**, 2504.

Ring nitrosation with nitrous acid is normally carried out only with active substrates such as amines and phenols.[65] However, primary aromatic amines give diazonium ions (reaction **2-33**, p. 484) when treated with nitrous acid, and secondary amines tend to give N-nitroso rather than C-nitroso compounds (reaction **2-35**, p. 486); hence this reaction is normally limited to phenols and tertiary aromatic amines. Nevertheless secondary aromatic amines may be C-nitrosated in two ways. The N-nitroso compound first obtained may be isomerized to a C-nitroso compound (the Fischer-Hepp rearrangement, **1-34**), or it may be treated with another mole of nitrous acid to give an N,C-dinitroso compound.

Much less work has been done on the mechanism of this reaction than on the preceding one. In some cases the attacking entity is NO^+, but in others it is apparently NOCl, NOBr, $H_2NO_2^+$, N_2O_3, etc., in each of which there is a carrier of NO^+. Evidence is that in many nitrosations NO^+ cannot be detected. NOCl and NOBr are formed during the normal process of making nitrous acid: the treatment of sodium nitrite with HCl or HBr.

OS **I**, 214, 411, 511; **II**, 223; **IV**, 247.

1-4 Diazonium coupling

$$\mathrm{ArH} + \mathrm{Ar'N_2^+} \longrightarrow \mathrm{Ar{-}N{=}N{-}Ar'}$$

Aromatic diazonium ions normally couple only with active substrates such as amines and phenols.[66] Presumably because of the size of the attacking species, substitution is mostly para to the activating group, unless that position is already occupied, in which case ortho substitution takes place. The fact that amines give ortho and para products shows that even in this acidic medium they are reacting in their un-ionized forms. However, if the acidity is too high, the reaction does not occur, because the concentration of free amine becomes too small. Primary and secondary amines face competition from attack at the nitrogen. However, the resulting N-azo compounds may be isomerized to C-azo compounds (reaction **1-35**). Acylated amines and phenolic esters are ordinarily not active enough for this reaction, though it is sometimes possible to couple them to diazonium ions containing electron-withdrawing groups in the para position, since such groups increase the concentration of the positive charge and thus the electrophilicity of the ArN_2^+.

OS **I**, 49, 374; **II**, 35, 39, 145.

1-5 Direct introduction of the diazonium group

$$\mathrm{ArH} \xrightarrow[\mathrm{HX}]{\mathrm{2HONO}} \mathrm{ArN_2^+} \quad \mathrm{X^-}$$

Diazonium salts may be prepared directly, by replacement of an aromatic hydrogen, without the necessity of going through the amino group.[67] The reaction is essentially limited to active substrates (amines and phenols), since otherwise poor yields are obtained. Besides this, if there is a substituent ortho to the activating group, the reaction is very slow.[68] Since the reagents and the substrate are the same as in reaction **1-3**, the first species to be formed is the nitroso compound. In the presence of excess nitrous acid, this is converted to the diazonium ion.[69]

---

[65] For a review, see de la Mare and Ridd, Ref. 1, pp. 94–104.

[66] For a review, see Zollinger, "Azo and Diazo Chemistry," pp. 210–265, Interscience Publishers, Inc., New York, 1961.

[67] Tedder, *J. Chem. Soc.* **1957**, 4003. For a review, see Belov and Kozlov, *Russ. Chem. Rev.* **32**, 59–75 (1963), pp. 61–62.

This reaction can also be performed on inactive substrates, even those containing a meta-directing group, if $HgSO_4$ is introduced as a catalyst, but the yields are lower.[70] The reaction pathway is entirely different in this case. The mercury salt attacks the ring to give $ArHg^+$, so that the NO^+ replaces Hg^{++} and not H^+.

1-6 Direct amination[71]

$$ArH + NH_2{-}O{-}SO_2{-}OH \xrightarrow{AlCl_3} ArNH_2$$

Aromatic compounds can be aminated by hydroxylamine-O-sulfonic acid,[72] but yields are fairly low, and the reaction is not often carried out. The mechanism has not been studied, but our knowledge of aromatic substitutions in general would lead us to suspect that the attacking entity is NH_2^+ or a carrier of it. Other reagents which might give rise to this kind of attacking entity have also been tried, e.g., salts of hydroxylamine,[73] but yields are no better. However, hydrazoic acid in the presence of $AlCl_3$ or sulfuric acid gave direct amination in yields of 10 to 65%.[74] N-Substituted hydroxylamine ethers (RNHOMe and R_2NOMe) have been employed, with Friedel-Crafts catalysts, in attempts to introduce directly the NHR and NR_2 groups.[75] Secondary amines *were* formed, in about 25% yield, but the method was not very practical for tertiary amines. However, tertiary amines have been prepared in fairly good yields (about 50 to 90%) by treatment of aromatic hydrocarbons with N-chlorodialkylamines, by heating in 96% sulfuric acid; or with $AlCl_3$ or $FeCl_3$ in nitroalkane solvents; or by irradiation.[76]

Unusual orientation has been reported for amination with haloamines and with NCl_3 in the presence of $AlCl_3$. For example, toluene gave predominantly meta amination.[77] It has been suggested that initial attack in this case is by Cl^+ and that NH_2^- adds to the resulting σ-complex, so that the initial reaction is addition to a carbon-carbon double bond, and that elimination of HCl follows:[78]

---

[68] Patel and Tedder, *J. Chem. Soc.* **1963**, 4889.

[69] Tedder and Theaker, *Tetrahedron* **5**, 288 (1959).

[70] Tedder and Theaker, *J. Chem. Soc.* **1957**, 4008.

[71] For a review, see Kovacic, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 1493–1506, Interscience Publishers, Inc., New York, 1964.

[72] Keller and Smith, *J. Am. Chem. Soc.* **66**, 1122 (1944).

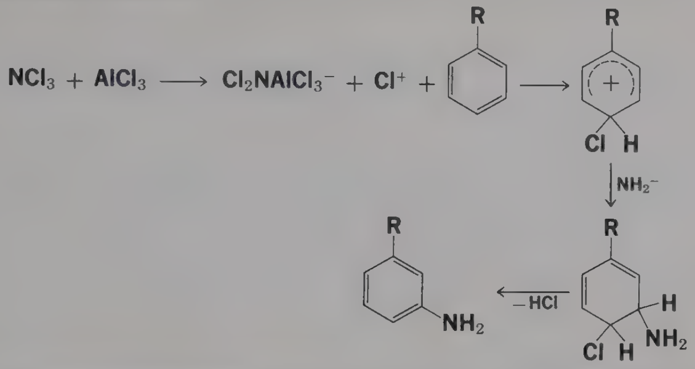
[73] Kovacic, Bennett, and Foote, *J. Org. Chem.* **26**, 3013 (1961); *J. Am. Chem. Soc.* **84**, 759 (1962).

[74] Kovacic, Russell, and Bennett, *J. Am. Chem. Soc.* **86**, 1588 (1964).

[75] Kovacic and Foote, *J. Am. Chem. Soc.* **83**, 743 (1961).

[76] Bock and Kompa, *Angew. Chem. Intern. Ed. Engl.* **4**, 783 (1965); *Chem. Ber.* **99**, 1347, 1357, 1361 (1966). Amination has also been effected by N-dichloroamines and reducing ions (such as Fe^{++} or Ti^{+++}) in a free-radical process: Minisci and Galli, *Tetrahedron Letters* **1965**, 433, **1966**, 2531; Minisci, Galli, and Cecere, *Tetrahedron Letters* **1965**, 4663.

[77] Kovacic, Lange, Foote, Goralski, Hiller, and Levisky, *J. Am. Chem. Soc.* **86**, 1650 (1964); Kovacic, Goralski, Hiller, Levisky, and Lange, *J. Am. Chem. Soc.* **87**, 1262 (1965); Kovacic, Levisky, and Goralski, *J. Am. Chem. Soc.* **88**, 100 (1966); Kovacic and Gormisch, *J. Am. Chem. Soc.* **88**, 3819 (1966).



Thus the actual electrophilic attack, according to this suggestion, is at the para position (or the ortho, which would lead to the same product), and the meta orientation of the amino group arises indirectly. This mechanism is called the *σ-substitution mechanism.*

Also see reactions **3-18** and **3-19** (p. 510).

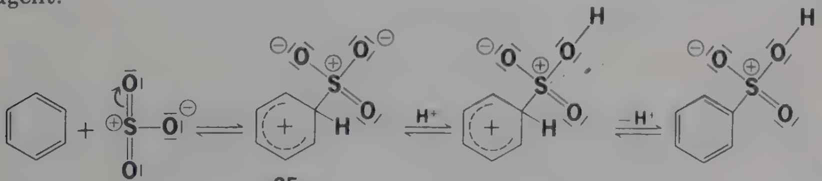
C. Sulfur electrophiles

1-7 Sulfonation

$$ArH + H_2SO_4 \longrightarrow ArSO_2OH$$

The sulfonation reaction is very broad in scope, and many aromatic hydrocarbons and halide derivatives have been sulfonated.[79] Sulfonation is often accomplished with concentrated sulfuric acid, but it may be done with fuming sulfuric acid, SO_3, $ClSO_2OH$, and other reagents. Since this is a reversible reaction (see reaction **1-44**), it may be necessary to drive the reaction to completion. However, at low temperatures the reverse reaction is very slow, and the forward reaction is then practically irreversible.[80] SO_3 reacts much more rapidly than sulfuric acid—with benzene it is nearly instantaneous. Sulfones are often side products. When sulfonation is carried out on a benzene ring containing four or five alkyl and/or halogen groups, rearrangements usually occur (see reaction **1-41**).

The electrophile is most probably SO_3, even when sulfuric acid is the reagent:



25

---

[78] Kovacic and Levisky, *J. Am. Chem. Soc.* **88**, 1000 (1966).

[79] For reviews, see Suter and Weston, *Org. Reactions* **3**, 141–197 (1946); Nelson, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 1355–1392, Interscience Publishers, Inc., New York, 1964; and Gilbert, "Sulfonation and Related Reactions," pp. 62–83, 87–124, Interscience Publishers, Inc., New York, 1965.

[80] Spryskov, *J. Gen. Chem. USSR* **30**, 2433 (1960).

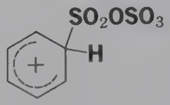
so that the intermediate becomes protonated between the normal first and second steps.[81] Evidence that the attacking entity is SO_3 is as follows:

1. A study of the reverse reaction[82] showed that the species which desulfonates is actually the ion $ArSO_2O^-$, and not the acid itself. By the principle of microscopic reversibility (p. 204), SO_3 and not SO_3H^+ must be the attacking species.
2. In D_2SO_4, DSO_3^+ is more abundant than HSO_3^+ is in H_2SO_4. Therefore, if HSO_3^+ were the attacking entity, the reaction should be faster in D_2SO_4. It is, however, slower.[81]
3. As was pointed out before, the rate with SO_3 is much greater than with H_2SO_4. Indeed, the rate is proportional to SO_3 concentration over a wide range of compositions of H_2O-H_2SO_4 to SO_3-H_2SO_4.[81]

However the conclusions as to mechanism in this reaction are not so certain as in nitration and halogenation.[83]

Sulfones are formed when **25** reacts with another molecule of SO_3 to give **26**, which acquires a proton and then attacks another aromatic ring.[84]

OS **II,** 42, 97, 482, 539; **III,** 288, 824; **IV,** 364.



26

1-8 Halosulfonation

$$ArH + ClSO_2OH \longrightarrow ArSO_2Cl$$

Aromatic sulfonyl chlorides can be prepared directly, by treatment of aromatic rings with chlorosulfuric acid.[85] Since sulfonic acids can also be prepared by the same reagent (reaction **1-7**), it is likely that they are intermediates, being converted to the halides by excess chlorosulfuric acid. The reaction has also been effected with bromo- and fluorosulfuric acids.

OS **I,** 8, 85.

1-9 Sulfurization

$$ArH + SCl_2 \xrightarrow{AlCl_3} ArSAr$$

Diaryl sulfides may be prepared by treating aromatic compounds with SCl_2 and a Friedel-Crafts catalyst. Other reagents which can bring about the same result are S_2Cl_2,[86] thionyl chloride, and even sulfur itself. A catalyst is not always necessary. The reaction has been used for ring closure:

---

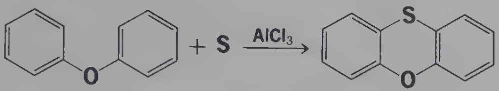
[81] Brand, Jarvie, and Horning, *J. Chem. Soc.* **1959,** 3844.

[82] Gold and Satchell, *J. Chem. Soc.* **1956,** 1635.

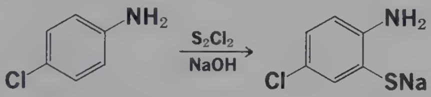
[83] See, for example, Kaandorp, Cerfontain, and Sixma, *Rec. trav. chim.* **81,** 969 (1962).

[84] Cerfontain, Hofman, and Telder, *Rec. trav. chim.* **83,** 493 (1964); Cerfontain, Telder, and Vollbracht, *Rec. trav. chim.* **83,** 1103 (1964).

[85] For a review, see Gilbert, Ref. 79, pp. 84–87.



When thionyl chloride is used, it is possible to obtain diaryl sulfoxides as the main products.[87] With certain substrates (primary amines with a chloro group, or a group not replaceable by chloro, in the para position), treatment with S_2Cl_2 and NaOH gives thiophenolate salts:



This is called the *Herz reaction.*[88]

OS **II**, 242, 485. Also see OS **I**, 574; **III**, 76.

1-10 Sulfonylation

$$\mathrm{ArH} + \mathrm{RSO_2Cl} \xrightarrow{\mathrm{AlCl_3}} \mathrm{ArSO_2R}$$

Aryl sulfones can be formed by treatment of aromatic compounds with sulfonyl halides and a Friedel-Crafts catalyst.[89] R may also be aryl. This reaction is analogous to Friedel-Crafts acylation with carboxylic acid halides (reaction **1-13**).

D. Halogen electrophiles

1-11 Halogenation[90]

1. *Chlorine and bromine*

$$\mathrm{ArH} + \mathrm{Br_2} \xrightarrow{\mathrm{Fe}} \mathrm{ArBr}$$

Aromatic compounds may be brominated or chlorinated by treatment with bromine or chlorine in the presence of a catalyst, most often iron. However, the real catalyst is not the iron itself, but the ferric bromide or ferric chloride formed in small amounts from the reaction between iron and the reagent. Ferric chloride and other Lewis acids are often directly used as catalysts, as is iodine. For active substrates such as amines or phenols, no catalyst is needed, and indeed the reaction is so rapid that it is carried out with a dilute solution of bromine or chlorine in water at room temperature. Even so, it is not possible with amines to stop the reaction before all of the available ortho and para positions are substituted. With phenols it is possible to stop after one group has entered. The rapid room-temperature reaction with amines and phenols is often used as a test for these compounds. Chlorine is a more active reagent than bromine.

---

[86] Both SCl_2 and S_2Cl_2 are known as sulfur chloride.

[87] Nikolenko and Krizhechkovskaya, *J. Gen. Chem. USSR* **33**, 3664 (1963); Oae and Zalut, *J. Am. Chem. Soc.* **82**, 5359 (1960).

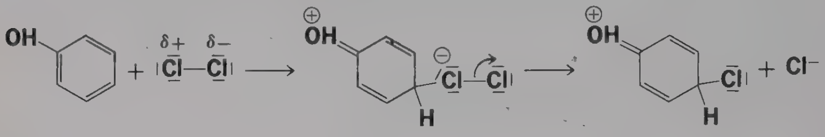
[88] For a review, see Warburton, *Chem. Rev.* **57**, 1011–1020 (1957).

[89] For a review, see Jensen and Goldman, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 1319–1353, Interscience Publishers, Inc., New York, 1964.

[90] For reviews, see de la Mare and Ridd, Ref. 1, pp. 105–148; Norman and Taylor, Ref. 1, pp. 119–155; and Braendlin and McBee, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 1517–1593, Interscience Publishers, Inc., New York, 1964.

Other reagents have also been used, for example, N-chloro amides, HOCl, *tert*-BuOCl, and N-bromosuccinimide. A particularly powerful reagent consists of S_2Cl_2 and $AlCl_3$ in sulfuryl chloride (SO_2Cl_2).[91] Halogenation has also been accomplished with benzoyl peroxide and lithium halide.[92] If the substrate contains alkyl groups, then side-chain halogenation (reaction **4-1**, p. 532) is possible with most of the reagents mentioned, including chlorine and bromine. Since side-chain halogenation is catalyzed by light, the reactions should be run in the absence of light wherever possible.

For reactions in the absence of a catalyst, the attacking entity is simply Br_2 or Cl_2 which has been polarized by the ring:[93]



27 **28**

Although the equation as written shows an intermediate which has two chlorines, the Cl—Cl bond may also be broken in the course of the attack, so that the only intermediate is **28.**

If **27** *is* present (note that the central chlorine has 10 electrons in its outer shell), then its stability may be such that an outside entity, such as the solvent, may be required to remove Cl^-. If this is the rate-determining step in these cases, then the rate should be different in different solvents. This has been shown to be the case.[94] Evidence for molecular chlorine or bromine as the attacking species in these cases is that acids, bases, and other ions, including especially chloride ion, accelerate the rate about equally, although if chlorine were dissociating into Cl^+ and Cl^-, the addition of chloride should decrease the rate, and acids should increase it.

When a Lewis acid catalyst is used along with chlorine or bromine, then the attacking entity is probably Cl^+ or Br^+, formed in this manner:

$$AlCl_3 + Br_2 \longrightarrow AlCl_3Br^- + Br^+$$

With other reagents, the attacking entity may be Cl^+ or Br^+, or it may be a species such as H_2OBr^+ (the conjugate acid of HOBr), in which H_2O is a carrier of Br^+ or Cl^+. When *tert*-BuOCl is the reagent, the attacking entity is Cl^+ in acidic solution and Cl_2 in nonacidic solution.[95] It has been demonstrated in the reaction between N-methylaniline and calcium hypochlorite that the chlorine attacking entity attacks the *nitrogen* to give N-chloro-N-methylaniline, which rearranges (as in reaction **1-36**) to give a mixture of ring-chlorinated N-methylanilines in which the ortho isomer predominates.[96] Infrared spectra of the reaction mixture showed a continuous disappearance of the N—H peak.

---

[91] Ballester, Molinet, and Castaner, *J. Am. Chem. Soc.* **82,** 4254 (1960).

[92] Kochi, Graybill, and Kurz, *J. Am. Chem. Soc.* **86,** 5257 (1964).

[93] For a review of the mechanism of halogenations, see Berliner, *J. Chem. Educ.* **43,** 124–132 (1966).

[94] Andrews and Keefer, *J. Am. Chem. Soc.* **81,** 1063 (1959).

[95] Harvey and Norman, *J. Chem. Soc.* **1961,** 3604.

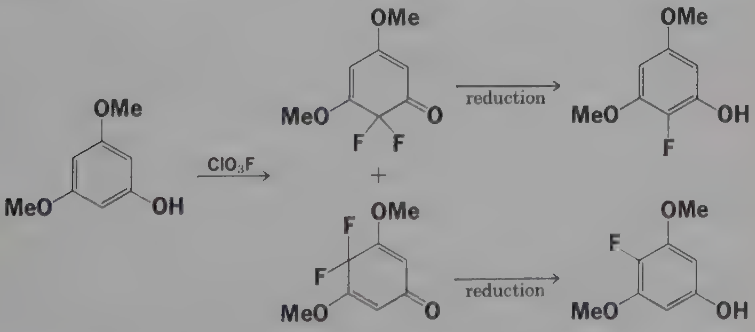
$FeCl_3$ itself,[97] and also $CuCl_2$, $SbCl_5$, etc.,[98] can give moderate yields of aryl chlorides.[99] The electrophiles here might be species such as $FeCl_2^+$.

When chlorination or bromination is carried out at high temperatures (e.g., 300 to 400°), ortho-para-directing groups direct meta, and vice versa.[100] A different mechanism is operating here, which is not completely understood.

2. *Iodine.* Iodine is the least reactive of the halogens in aromatic substitution, and reversibility is important enough so that iodination is seldom feasible unless some species is present to remove iodide ion as soon as it is formed. When the substrate is an aromatic amine, the reaction occurs because the iodide precipitates as the salt. Otherwise an oxidizing agent must be added. Examples are HNO_3, HIO_3, and H_2O_2, which oxidize the iodide ion to iodine. ICl is a better iodinating agent than iodine itself.

The actual attacking species is less clear in this case than with bromine or chlorine. There are good reasons for believing that I^+ is the electrophile in most situations. Iodine itself is probably too unreactive, except for active species such as phenols, where there is good evidence that I_2 is the attacking entity.[101] There is evidence that AcOI may be the attacking entity when peroxyacetic acid is the catalyst.[102]

3. *Fluorine.* Fluorine is too reactive for the fluorination of aromatic rings. However, ClO_3F attacks phenols[103] to give *gem*-difluoro products, which can be reduced to give what amounts to overall substitution of fluorine for hydrogen:



This is presumed to be an electrophilic process.

---

[96] Haberfield and Paul, *J. Am. Chem. Soc.* **87,** 5502 (1965).

[97] Kovacic, Wu, and Stewart, *J. Am. Chem. Soc.* **82,** 1917 (1960).

[98] Ware and Borchert, *J. Org. Chem.* **26,** 2263, 2267 (1961).

[99] For a review of halogenations with metal halides, see Kovacic, in Olah, "Friedel-Crafts and Related Reactions," vol. IV, pp. 111-126, Interscience Publishers, Inc., New York, 1965.

[100] For a review of this type of reaction, see Kooyman, *Pure Appl. Chem.* **7,** 193-202 (1963).

[101] Grovenstein and Aprahamian, *J. Am. Chem. Soc.* **84,** 212 (1962).

[102] Ogata and Nakajima, *Tetrahedron* **20,** 43, 2751 (1964).

[103] Taub, *Chem. Ind. (London)* **1962,** 558; Mills, Barrera, Olivares, and Garcia, *J. Am. Chem. Soc.* **82,** 5882 (1960).

The overall effectiveness of reagents in aromatic substitution is $Cl_2 > BrCl > Br_2 > ICl > I_2$.

OS **I,** 111, 121, 123, 128, 207, 323; **II,** 95, 97, 100, 173, 196, 343, 347, 349, 357, 592; **III,** 132, 134, 138, 262, 267, 575, 796; **IV,** 114, 166, 256, 545, 547, 872, 947; **40,** 7; **43,** 15; **44,** 34. Also see OS **II,** 128.

E. Carbon electrophiles. In the reactions in this section, a new carbon-carbon bond is formed. With respect to the aromatic ring they are electrophilic substitutions, since a positive species attacks the ring, and we treat them in this manner because it is customary. However, with respect to the electrophile most of these reactions are nucleophilic substitutions, and what was said in Chapter 10 is pertinent to them. Some are not substitutions with respect to the reagent. For example, reaction **1-12,** when performed with an olefin as reagent, is addition to a C=C double bond, and reaction **1-24** is addition to a C=O double bond.

1-12 Friedel-Crafts alkylation

$$\mathrm{ArH + RCl \xrightarrow{AlCl_3} ArR}$$

The alkylation of aromatic rings, called *Friedel-Crafts alkylation,* is a reaction of very broad scope.[104] The most important reagents are alkyl halides, olefins, and alcohols, but many other types of reagent have also been employed.[104] When alkyl halides are used, the reactivity is in the order F > Cl > Br > I, and, for example, $FCH_2CH_2CH_2Cl$ reacts with benzene to give $PhCH_2CH_2CH_2Cl$,[105] when the catalyst is BF_3. By the use of this catalyst it is therefore possible to place a halo alkyl group on a ring (see also reaction **1-25**).[106] Di- and trihalides, when all the halogens are the same, usually react with more than one molecule of aromatic compound, and it is usually not possible to stop the reaction earlier. Thus, benzene with CH_2Cl_2 gives, not $PhCH_2Cl$, but Ph_2CH_2; and benzene with $CHCl_3$ gives Ph_3CH. With CCl_4, however, the reaction stops when only three rings have been substituted, and the product is Ph_3CCl.

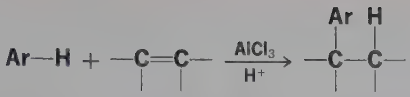
Olefins are especially good alkylating agents. With respect to them the reaction is addition of ArH to a C=C double bond:

---

[104] For a treatise on Friedel-Crafts reactions in general, see Olah, "Friedel-Crafts and Related Reactions," Interscience Publishers, Inc., New York, 1963–1965. Volume 1 covers general aspects: such things as catalyst activity, intermediate complexes, etc. Volume 2 covers alkylation and related reactions. In this volume the various reagents are treated by the indicated authors as follows: alkenes and alkanes, Patinkin and Friedman, pp. 1–288; dienes and substituted alkenes, Koncos and Friedman, pp. 289–412; alkynes, Franzen, pp. 413–416; alkyl halides, Drahowzal, pp. 417–475; alcohols and ethers, Schriesheim, pp. 477–595; sulfonates and inorganic esters, Drahowzal, pp. 641–658. Review articles are by Price, *Org. Reactions* **3,** 1–82 (1946); Baddeley, *Quart. Rev. (London)* **8,** 355–379 (1954); Roberts, *Chem. Eng. News* **43,** No. 4, 96–112 (Jan. 25, 1965); and Norman and Taylor, Ref. 1, pp. 156–173.

[105] Olah and Kuhn, *J. Org. Chem.* **29,** 2317 (1964).

[106] For a review of selectivity in this reaction, i.e., which group preferentially attacks when the reagent contains two or more, see Olah, in Olah, Ref. 104, vol. 1, pp. 881–905. This review also covers the case of alkylation versus acylation.



$$\mathrm{Ar{-}H} + -\underset{|}{\mathrm{C}}{=}\underset{|}{\mathrm{C}}- \xrightarrow[\mathrm{H^+}]{\mathrm{AlCl_3}} -\overset{\overset{\mathrm{Ar}}{|}}{\underset{|}{\mathrm{C}}}-\overset{\overset{\mathrm{H}}{|}}{\underset{|}{\mathrm{C}}}-$$

Acetylene reacts with two moles of aromatic compound to give 1,1-diarylethanes, but other alkynes react poorly if at all. Alcohols are more active than alkyl halides, though if a Lewis acid catalyst is used, more catalyst is required, since the catalyst complexes with the OH group. However, proton acids, especially H_2SO_4, are often used to catalyze alkylation with alcohols. When esters are the reagents, there is competition between alkylation and acylation (reaction **1-14**). Though this competition may often be controlled by choice of catalyst, and alkylation is usually favored, esters are not often employed in Friedel-Crafts reactions. Other alkylating agents are ethers, mercaptans, sulfides, thiocyanates, sulfates, sulfonates, and even alkanes and cycloalkanes, under conditions where these are converted to carbonium ions. Notable here are ethylene oxide, which puts the CH_2CH_2OH group onto the ring, and cyclopropane. For all types of reagent the reactivity order is allyl, benzyl type > tertiary > secondary > primary.

Regardless of which reagent is used, a catalyst is always required. Aluminum chloride is the most common, but many other Lewis acids have been used, and also proton acids such as HF and H_2SO_4.[107] For active halides a trace of a less active catalyst, for example, $ZnCl_2$, may be enough. For an unreactive halide, such as methyl chloride, a more powerful catalyst is needed, for example, $AlCl_3$, and in larger amounts. In some cases, especially with olefins, a Lewis acid catalyst causes reaction only if a small amount of proton-donating cocatalyst is present. Catalysts have been arranged in the following order of overall reactivity: $AlBr_3 > AlCl_3 > GaCl_3 > FeCl_3 > SbCl_5 > ZrCl_4$, $SnCl_4 > BCl_3$, BF_3, $SbCl_3$,[108] but the reactivity order in each case depends on the substrate, reagent, and conditions. A survey of the field has shown that "in all probability in Friedel-Crafts type reactions no simple monotonic series of catalytic activity of Lewis acid and related proton acid catalysis is possible."[109] The most common solvent for Friedel-Crafts alkylation is carbon disulfide.

Friedel-Crafts alkylation is unusual among the principal aromatic substitutions in that the entering group is activating, so that di- and polyalkylation are frequently observed. However, the activating effect of simple alkyl groups (e.g., ethyl, isopropyl) is such that compounds with these groups as substituents are attacked in Friedel-Crafts alkylations only about 1.5 to 3 times as fast as benzene,[110] and so it is often possible to get high yields of monoalkyl product. Actually the fact that di- and polyalkyl derivatives are frequently obtained is not due to the small difference in reactivity, but to the circumstance that alkylbenzenes are preferentially soluble in the catalyst layer, where the reaction is actually taking place.[111] This factor may be removed by the use of a suitable solvent, by high temperatures, or by high-speed stirring.

---

[107] For a review of catalysts and solvents in Friedel-Crafts reactions, see Olah, in Olah, Ref. 104, vol. 1, pp. 201–366, 853–81.

[108] Russell, *J. Am. Chem. Soc.* **81**, 4834 (1959).

[109] Ref. 107, p. 859.

[110] Condon, *J. Am. Chem. Soc.* **70**, 2265 (1948); Olah, Kuhn, and Flood, *J. Am. Chem. Soc.* **84**, 1688 (1962).

Also unusual is the fact that the OH, OR, NH_2, etc., groups do not facilitate the reaction, since the catalyst coordinates with these basic groups. Although phenols give the usual Friedel-Crafts reactions, orienting ortho and para, the reaction is very poor for amines. However, amines can undergo the reaction, if olefins are used as reagents and aluminum anilides as catalysts.[112] In this method the catalyst is prepared by treating the amine to be alkylated with $\frac{1}{3}$ mole of $AlCl_3$. A similar reaction may be performed with phenols, although here the catalyst is $Al(OAr)_3$.[113]

Naphthalene gives poor yields in Friedel-Crafts alkylation, because it is so active that it reacts with the catalyst. Heterocyclic rings are usually also poor substrates for the reaction. Furan, thiophene, and pyridine cannot usually be alkylated. Although some furans and thiophenes have been alkylated, a true alkylation of a pyridine or a quinoline has never been described.[114]

In most cases, meta-directing groups make the ring too inactive for alkylation. Nitrobenzene cannot be alkylated, and there are only a few reports of successful Friedel-Crafts alkylations when electron-withdrawing groups are present.[115] This is not because the attacking species is not powerful enough; indeed we have seen (p. 394) that alkyl carbonium ions are among the most powerful of electrophiles. The difficulty is caused by the fact that, with inactive substrates, degradation and polymerization of the electrophile occurs before it can attack the ring. However, if an activating and a deactivating group are both present on a ring, Friedel-Crafts alkylation can be accomplished.[116] Aromatic nitro compounds can be methylated by a nucleophilic mechanism (reaction **3-17**).

An important synthetic limitation of Friedel-Crafts alkylation is that rearrangement frequently takes place in the reagent. For example, benzene treated with *n*-propyl bromide gives mostly isopropylbenzene (cumene) and much less *n*-propylbenzene. Rearrangement is usually in the order primary → secondary → tertiary and occurs mostly by migration of H^-, but also of R^- (see discussion of rearrangement mechanisms in Chapter 18). However, conditions can often be chosen to minimize this. For example, benzene, when treated with *n*-propyl chloride at room temperature, gives mostly *n*-propylbenzene; and straight-chain alcohols usually do not rearrange when the catalyst is $AlCl_3$, though they do with BF_3[117] or H_2SO_4.[118] There are two possible explanations for this absence of rearrangement under some conditions: either the reactions in these cases do not proceed by free carbonium ions, or the carbonium ions attack before they have time to rearrange. In this connection it should be remembered that primary cations, being less stable than tertiary, are therefore more reactive. What is perhaps more difficult to explain is that some rearrangements have been reported to go the other way: tertiary → secondary → primary. For example, treatment of *p*-cresol with 2-chloro-2-methylbutane and BF_3 gave 15 to 20% **29**, but also 10 to 15% **30**.[119] This

---

[111] Francis, *Chem. Rev.* **43**, 257 (1948).

[112] For a review, see Stroh, Ebersberger, Haberland, and Hahn, in Foerst, "Newer Methods of Preparative Organic Chemistry," vol. 2, pp. 227–252, Academic Press Inc., New York, 1963. This article also appeared in *Angew. Chem.* **69**, 124–131 (1957).

[113] For a review, see Stroh, Seydel, and Hahn, in Foerst, "Newer Methods of Preparative Organic Chemistry," vol. 2, pp. 337–359, Academic Press Inc., New York, 1963. This article also appeared in *Angew. Chem.* **69**, 669–706 (1957).

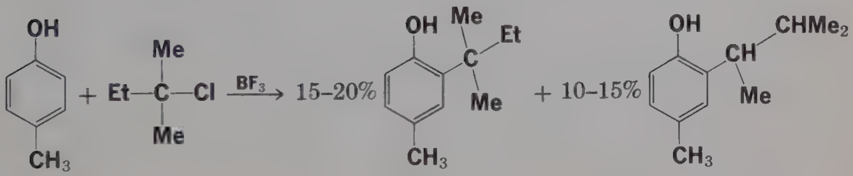
[114] Drahowzal, in Olah, Ref. 104, vol. 2, p. 433.

[115] Campbell and Spaeth, *J. Am. Chem. Soc.* **81**, 5933 (1959).

[116] Olah, in Olah, Ref. 104, vol. 1, p. 34.

[117] Streitwieser, Stevenson, and Shaeffer, *J. Am. Chem. Soc.* **81**, 1110 (1959); Streitwieser, Shaeffer, and Andreades, *J. Am. Chem. Soc.* **81**, 1113 (1959).

[118] Ioffe and Yan, *J. Gen. Chem. USSR* **33**, 2141 (1963).

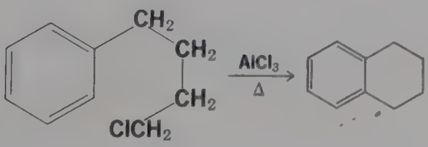


29 **30**

may be a case of thermodynamic control of the products rather than kinetic control. Apparently the order of *thermodynamic* stability of the alkylbenzenes is primary > secondary > tertiary.[120]

Because of the rearrangements which usually accompany alkylation with primary reagents, *n*-alkylbenzenes are often prepared by *acylation* (reaction **1-14**) followed by Clemmensen or Wolff-Kishner reduction (reaction **9-34**, p. 891). However, rearrangements are not the only reason for using this alternate approach. Alkylation is more active than acylation, and therefore less selective. For example, toluene with ethyl bromide and $GaBr_3$ gave 38.4% *o*-ethyltoluene, 40.6% of the para isomer, and 21.0% of the meta isomer, while acylation gave 97.6% *p*-methylacetophenone.[121] Hence, even in this case, where isomerization is not a factor, it is profitable to acylate and reduce, rather than to separate the mixture of isomers.

An important use of the Friedel-Crafts alkylation reaction is to effect ring closure.[122] The most common method is to heat with aluminum chloride an aromatic compound having a halogen, hydroxy, or olefinic group in the proper position, as, for example, in the preparation of tetralin:



Another way of effecting ring closure through Friedel-Crafts alkylation is to use a reagent containing two groups, for example:

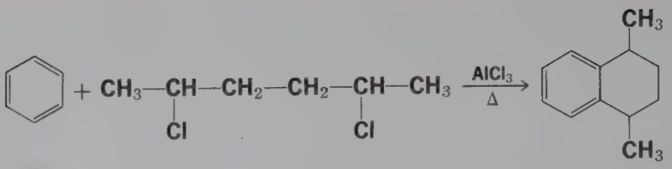
---

[119] Malchick and Hannan, *J. Am. Chem. Soc.* **81**, 2119 (1959).

[120] Olah, in Olah, Ref. 104, vol. 1, p. 70.

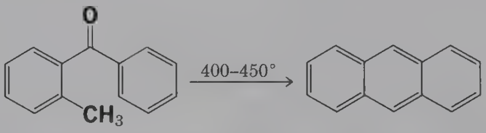
[121] Stock and Brown, *Advan. Phys. Org. Chem.* **1**, 46–47 (1963).

[122] For a review, see Barclay, in Olah, Ref. 104, vol. 2, pp. 785–977.



These reactions are most successful for the preparation of six-membered rings,[123] though five- and seven-membered rings have also been closed in this manner.

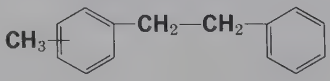
A ring-closure reaction which is somewhat similar is called the *Elbs reaction.*[124] Diaryl ketones containing an ortho methyl group can be cyclized by heating, although the yields are usually quite low:



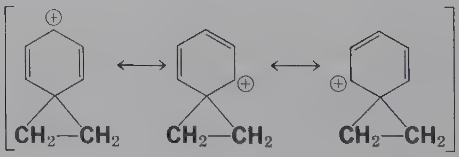
Since water is lost, this is a cyclodehydration. Since the reaction requires no catalyst, it is probably not a true Friedel-Crafts reaction. The value of the reaction is that it can be used to prepare compounds, even in low yields, that are very difficult to prepare any other way.

For other Friedel-Crafts ring-closure reactions see reactions **1-13, 1-14,** and **1-24.**

From what has been said thus far it is evident that the electrophile in Friedel-Crafts alkylation is a carbonium ion, at least in most cases. This is in accord with the knowledge that carbonium ions rearrange in the direction primary → secondary → tertiary (see Chapter 18). Other evidence that carbonium ions are the attacking species is that the use of $PhCH_2{}^{14}CH_2Cl$ as the reagent in the Friedel-Crafts alkylation of toluene gave a product (**31**) in which each of the ethane carbons possessed about 50% of the labeling.[125] This indicates the formation of $PhCH_2CH_2{}^+$, which is stabilized by conversion to the nonclassical **32**.



31



32

---

[123] See Khalaf and Roberts, *J. Org. Chem.* **31,** 89 (1966).

[124] For a review, see Fieser, *Org. Reactions* **1,** 129–154 (1942).

[125] McMahon and Bunce, *J. Org. Chem.* **29,** 1515 (1964).

In each case the carbonium ion may be formed from the attacking reagent and the catalyst. For the three most important types of reagent these reactions are:

From alkyl halides:

$$\mathrm{RCl} + \mathrm{AlCl_3} \longrightarrow \mathrm{R^+} + \mathrm{AlCl_4^-}$$

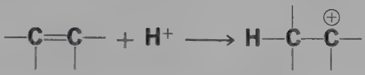
From alcohols and Lewis acids:

$$\mathrm{ROH} + \mathrm{AlCl_3} \longrightarrow \mathrm{ROAlCl_2} \longrightarrow \mathrm{R^+} + {}^-\mathrm{OAlCl_2}$$

From alcohols and proton acids:

$$\mathrm{ROH} + \mathrm{H^+} \longrightarrow \mathrm{ROH_2^+} \longrightarrow \mathrm{R^+} + \mathrm{H_2O}$$

From olefins (a supply of protons is always required):



$$-\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}- + \mathrm{H^+} \longrightarrow \mathrm{H}-\overset{|}{\underset{|}{\mathrm{C}}}-\overset{\oplus}{\underset{|}{\mathrm{C}}}-$$

In the case of olefins, Markovnikov's rule (p. 576) is followed. Alkylation has also been effected by carbonium ions generated by the diazotization of primary amines (see p. 290).[126] Carbonium-ion formation is particularly easy from some reagents, because of the stability of the cations. Triphenylmethyl chloride alkylates activated aromatic rings (e.g., phenols, amines) with no catalyst or solvent.[127] When the triphenylmethyl cation is generated from triphenylcarbinol and acid, the reaction is called the *Baeyer-Villiger condensation*, not to be confused with the Baeyer-Villiger rearrangement (reaction **8-20**, p. 822). Ions as stable as this are less reactive than other carbonium ions and often attack only active substrates. The tropylium ion, for example, alkylates anisole, but not benzene.[128]

In some cases, especially with primary reagents, the carbonium ion is not completely free but exists as an ion pair with, say, $\mathrm{AlCl_4^-}$, or as a complex. Evidence for this is that the same alkyl halide is often more reactive with $\mathrm{AlCl_3}$ than with $\mathrm{FeCl_3}$. Other evidence is that, in some cases, the reaction kinetics are third order: first order each in aromatic substrate, attacking reagent, and catalyst.[129] In these instances a mechanism in which the carbonium ion is slowly formed and then rapidly attacks the ring is ruled out, since, in such a mechanism, the substrate would not appear in the rate expression. Since it is known that free carbonium ions, once formed, rapidly attack the ring, there are no free carbonium ions here. It is also possible that, by a kind of S_N2 mechanism (with respect to the alkyl halide), there is attack by the ring on a complex between the halide and the catalyst.

---

[126] Pearson, Breder, and Craig, *J. Am. Chem. Soc.* **86,** 5054 (1964); Olah, Overchuk, and Lapierre, *J. Am. Chem. Soc.* **87,** 5785 (1965); Jurewicz, Bayless, and Friedman, *J. Am. Chem. Soc.* **87,** 5788 (1965).

[127] See, for example, Chuchani, *J. Chem. Soc.* **1960,** 325; Hart and Cassis, *J. Am. Chem. Soc.* **76,** 1634 (1954); Hickinbottom, *J. Chem. Soc.* **1934,** 1700; Chuchani and Zabicky, *J. Chem. Soc. (C)* **1966,** 297.

[128] Bryce-Smith and Perkins, *J. Chem. Soc.* **1962,** 5295.

[129] For examples, see Brown and Grayson, *J. Am. Chem. Soc.* **75,** 6285 (1953); Jungk, Smoot, and Brown, *J. Am. Chem. Soc.* **78,** 2185 (1956); Choi and Brown, *J. Am. Chem. Soc.* **85,** 2596 (1963).

Rearrangement is possible even with a non-carbonium-ion mechanism. The rearrangement could occur *before* the attack on the ring takes place at all. It has been shown that treatment of $CH_3{}^{14}CH_2Br$ with $AlBr_3$, *in the absence of any aromatic compound,* gave a mixture of the starting material and $^{14}CH_2CH_2Br$.[130] Similar results were obtained with $PhCH_2{}^{14}CH_2Br$, in which case the rearrangement was so fast that the rate could be measured only below −70°. Rearrangement could also occur *after* formation of the product, since alkylation is reversible (see reaction **1-38**).[131] If there are ion pairs present, rearrangement may take place by hydride-ion shift, without disturbing the ion-pair relationship.[132]

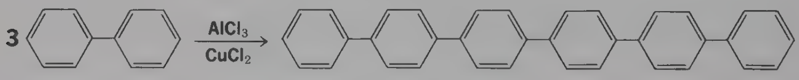
See reaction **4-17** (p. 553) for *free-radical* alkylation.

OS **I**, 95, 548; **II**, 151, 229, 232, 236, 248; **III**, 343, 347, 504, 842; **IV**, 47, 520, 620, 665, 702, 898, 960; **44**, 64.

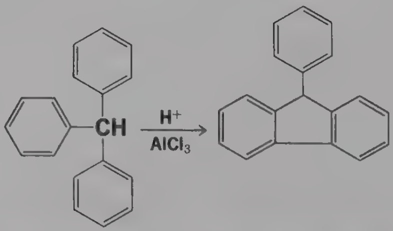
1-13 Friedel-Crafts arylation. The Scholl reaction

$$2\text{ArH} \xrightarrow[\text{H}^+]{\text{AlCl}_3} \text{Ar—Ar} + \text{H}_2$$

The coupling of two aromatic molecules by treatment with a Lewis acid and a proton acid is called the *Scholl reaction.*[133] Yields are low, and the synthesis is seldom useful. High temperatures and strong acid catalysts are required, and the reaction fails for substrates which are destroyed by these conditions. Because the reaction becomes important with large fused ring systems, ordinary Friedel-Crafts reactions (**1-12**) on these systems are rare. For example, naphthalene gives binaphthyl under Friedel-Crafts conditions. Yields may be increased by the addition of a salt such as $CuCl_2$ or $FeCl_3$, which acts as an oxidant.[134] Thus biphenyl gave more than 50% *p*-sexiphenyl upon treatment at 80° with $AlCl_3$ and $CuCl_2$:[135]



Intramolecular Scholl reactions, e.g.,



---

[130] Sixma and Hendriks, *Rec. trav. chim.* **75**, 169 (1956); Adema and Sixma, *Rec. trav. chim.* **81**, 323, 336 (1962).

[131] For an example, see Lee, Hamblin, and Uthe, *Can. J. Chem.* **42**, 1771 (1964).

[132] For an example, see Douwes and Kooyman, *Rec. trav. chim.* **83**, 276 (1964).

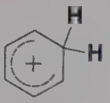
[133] For a review, see Balaban and Nenitzescu, in Olah, Ref. 104, vol. 2, pp. 979–1047.

[134] Kovacic and Koch, *J. Org. Chem.* **28**, 1864 (1963), **30**, 3176 (1965); Kovacic and Kyriakis, *J. Am. Chem. Soc.* **85**, 454 (1963); Kovacic and Wu, *J. Org. Chem.* **26**, 759, 762 (1961).

[135] Kovacic and Lange, *J. Org. Chem.* **29**, 2416 (1964).

are much more successful than the intermolecular kind. There are some who apply the term Scholl reaction only to the intramolecular type.

The mechanism is not clear, but it may involve attack by a proton to give **33**, which would then be the electrophile which attacks the other ring.



33

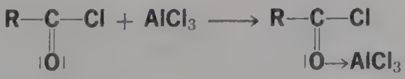
Sometimes arylations have been accomplished by treating aromatic substrates with particularly active aryl halides, especially fluorides. For free-radical arylations, see reactions **4-15** (p. 550) and **4-17** (p. 553).

OS **IV**, 482. Also see OS **45**, 91; **46**, 5.

1-14 Friedel-Crafts acylation

$$\mathrm{ArH + RCOCl \xrightarrow{AlCl_3} ArCOR}$$

The most important method for the preparation of aryl ketones is known as *Friedel-Crafts acylation.*[136] The reaction is of wide scope. Reagents used are not only acyl halides, but also carboxylic acids, anhydrides, and ketenes. Esters usually give predominant alkylation (see reaction **1-12**). R may be aryl as well as alkyl. Rearrangement of R is never found, whether R is straight-chain or branched. All four acyl halides may be used, though chlorides are most commonly employed. The order of activity is usually, but not always, $I > Br > Cl > F$.[137] Catalysts are Lewis acids, similar to those in reaction **1-12**, but in acylation a little more than 1 mole of catalyst is required per mole of reagent, since the first mole coordinates with the oxygen of the reagent:[138]



$$\mathrm{R{-}\underset{\underset{|O|}{\|}}{C}{-}Cl + AlCl_3 \longrightarrow R{-}\underset{\underset{|O\rightarrow AlCl_3}{\|}}{C}{-}Cl}$$

Frequently this 1:1 complex is separately prepared and then the aromatic compound added.

The reaction is quite successful for many types of substrate, including fused ring systems, which give poor results in reaction **1-12**. Compounds containing ortho-para-directing groups, including alkyl, hydroxy, alkoxy, halogen, and acetamido groups, are easily acylated and give mainly or exclusively the para products, because of the relatively large size of the acyl group. However, aromatic amines give poor results. With amines and phenols there may be competition from N- or O-acylation; however, O-acylated phenols can be converted to C-acylated phenols by the Fries rearrangement (reaction **1-31**). Friedel-Crafts acylation is usually prevented by meta-directing groups. Many heterocyclic systems, including furans, thiophenes, pyrans, and pyrroles, but not pyridines or quinolines, may be acylated in good yield. Gore, in Reference 136 (pp. 36–100; with tables, pp. 105–321), presents an exhaustive summary of the substrates to which this reaction has been applied.

---

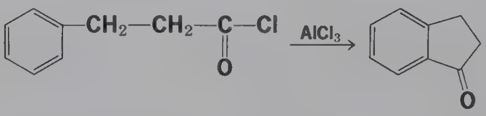
[136] For reviews of Friedel-Crafts acylation, see Olah, "Friedel-Crafts and Related Reactions," Interscience Publishers, Inc., New York, 1963–1964, as follows: vol. 1, Olah, pp. 91–115; vol. 3, Gore, pp. 1–381; Peto, pp. 535–910; Sethna, pp. 911–1002; and Jensen and Goldman, pp. 1003–1032. Other reviews are by Baddeley, *Quart. Rev.* (*London*) **8**, 355–379 (1954); Gore, *Chem. Rev.* **55**, 229–281 (1955); and Norman and Taylor, Ref. 1, pp. 174–182.

[137] Yamase, *Bull. Chem. Soc. Japan* **34**, 480 (1961); Corriu, *Bull. Soc. chim. France* **1965**, 821.

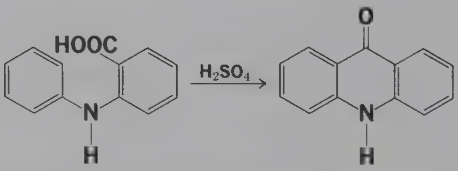
[138] The crystal structure of this complex has been reported by Rasmussen and Broch, *Acta Chem. Scand.* **20**, 1351 (1966).

When a mixed anhydride RCOOCOR′ is the reagent, it is possible to get two products, ArCOR and ArCOR′. Which product predominates depends on two factors. If R contains electron-withdrawing groups, then ArCOR′ is chiefly formed, but if this factor is approximately constant in R and R′, then the ketone with the larger R group predominantly forms.[139] This means that *formylations* of the ring do not occur with mixed anhydrides of formic acid, HCOOCOR.

An important use of the Friedel-Crafts acylation reaction is to effect ring closure.[140] This may be done if an acyl halide, anhydride, or acid group is in the proper position. An example is



The reaction is mostly used to close six-membered rings but has also been done for five- and seven-membered rings, which close less readily. Even larger rings may be closed by high-dilution techniques.[141] Tricyclic and larger systems are often made by using substrates containing one of the acyl groups on a ring, an example being the formation of acridone:



Many fused ring systems are made in this manner. If the bridging group is CO, then the product is a quinone. One of the most common catalysts for intramolecular Friedel-Crafts acylation is polyphosphoric acid,[142] but $AlCl_3$, H_2SO_4, and other Lewis and proton acids are also used, though acylations with acyl halides are not generally catalyzed by proton acids.

Friedel-Crafts acylation is often carried out with cyclic anhydrides,[143] in which case the product contains a carboxyl group in the side chain. When succinic anhydride is used, the product is $ArCOCH_2CH_2COOH$. This can be reduced (reaction **9-34**, p. 891) to $ArCH_2CH_2CH_2COOH$, which can then be cyclized by an internal Friedel-Crafts acylation. The total process is called the *Haworth reaction:*

---

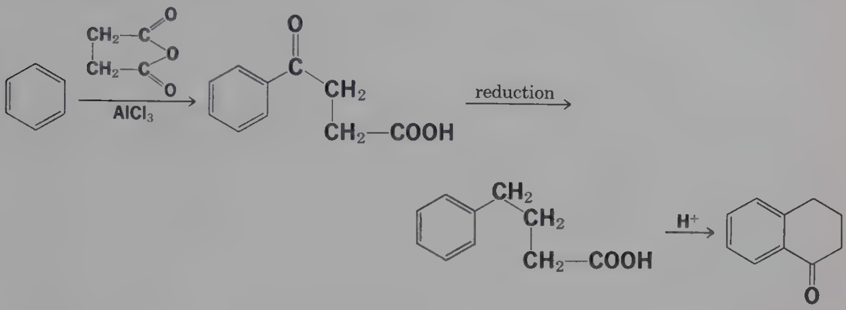
[139] Edwards and Sibelle, *J. Org. Chem.* **28**, 674 (1963).

[140] For reviews, see Johnson, *Org. Reactions* **2**, 114–177 (1944); and Sethna, Ref. 136.

[141] For example, see Schubert, Sweeney, and Latourette, *J. Am. Chem. Soc.* **76**, 5462 (1954).

[142] The use of this catalyst is reviewed by Uhlig and Snyder, *Advan. Org. Chem.* **1**, 35–81 (1960).

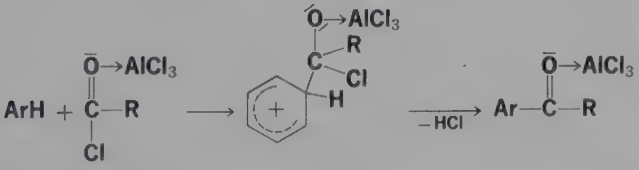
[143] For reviews, see Berliner, *Org. Reactions* **5**, 229–289 (1949); and Peto, Ref. 136.



The mechanism of Friedel-Crafts acylation is not completely understood, but at least two mechanisms probably operate, depending on conditions. In most cases the attacking species is the acyl cation, either free or as an ion pair, formed by[144]

$$RCOCl + AlCl_3 \longrightarrow RCO^+ + AlCl_4^-$$

However, there is evidence that, under some conditions, it is the 1:1 complex which attacks:



Free-ion attack is more likely for sterically hindered R.[145] The ion CH_3CO^+ has been detected (by infrared spectroscopy) in the liquid complex between acetyl chloride and aluminum chloride, and in polar solvents such as nitrobenzene; but in nonpolar solvents such as chloroform only the complex, and not the free ion, is present.[146] In any event, 1 mole of catalyst certainly remains complexed to the product at the end of the reaction. When acids or anhydrides are reagents, they are converted by the catalyst to acyl halides, which are the actual reactants. When the reaction is performed with $RCO^+ \quad SbF_6^-$, no catalyst is required, and the free ion (or ion pair) is undoubtedly the attacking entity.[147]

---

[144] After two minutes, exchange between PhCOCl and $Al(^{36}Cl)_3$ is complete: Oulevey and Susz, *Helv. Chim. Acta* **47,** 1828 (1964).

[145] Yamase, *Bull. Chem. Soc. Japan* **34,** 484 (1961); Gore, *Bull. Chem. Soc. Japan* **35,** 1627 (1962); Satchell, *J. Chem. Soc.* **1961,** 5404.

[146] Cook, *Can. J. Chem.* **37,** 48 (1959).

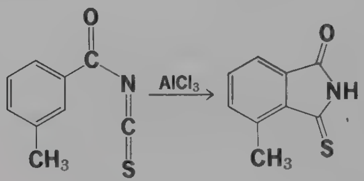
[147] Olah, Kuhn, Flood, and Hardie, *J. Am. Chem. Soc.* **86,** 2203 (1964).

OS **I**, 109, 353, 476, 517; **II**, 3, 8, 15, 81, 156, 169, 304, 520, 569; **III**, 6, 14, 23, 53, 109, 183, 248, 272, 593, 637, 761, 798; **IV**, 8, 34, 88, 898, 900; **41**, 1.

1-15 Amidation with isocyanates

$$\text{ArH} + \text{RNCO} \xrightarrow{\text{AlCl}_3} \text{ArCONHR}$$

N-Substituted amides can be prepared by direct attack of isocyanates on aromatic rings.[148] R may be alkyl or aryl, but if the latter, dimers and trimers are also obtained. Isothiocyanates similarly give thioamides. The reaction has been carried out intramolecularly both with aralkyl isothiocyanates and acyl isothiocyanates.[149] In the latter case, the product is easily hydrolyzable to a dicarboxylic acid; therefore this represents a way of putting a carboxyl group on a ring ortho to one which is already there (**34** is prepared by treatment of the acyl halide with lead thiocyanate). The reaction gives better yields with substrates of the type $\text{ArCH}_2\text{CONCS}$, where six-membered rings are formed.



34

OS **44**, 91.

Reactions **1-16** through **1-21** are direct formylations of the ring.[150] Reaction **1-14** has not been used for formylation, since neither formic anhydride nor formyl chloride is stable at ordinary temperatures. Formyl chloride has been shown to be stable in chloroform solution for 1 hr at −60°,[151] but it is not useful for formylating aromatic rings under these conditions. Formic anhydride has been prepared in impure form, but it slowly decomposes at room temperature.[152] It has not yet been used for aromatic formylations. Mixed anhydrides of formic and other acids are known[153] and can be used to formylate amines (see reaction **0-52**, p. 336) and alcohols, but when they are applied to aromatic rings, no formylation takes place (p. 414).

---

[148] Effenberger and Gleiter, *Chem. Ber.* **97**, 472 (1964).

[149] Smith and Kan, *J. Am. Chem. Soc.* **82**, 4753 (1960), *J. Org. Chem.* **29**, 2261 (1964).

[150] For a review, see Olah and Kuhn, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 1153–1256, Interscience Publishers, Inc., New York, 1964.

[151] Staab and Datta, *Angew. Chem. Intern. Ed. Engl.* **3**, 132 (1964).

[152] Schijf, Scheeren, van Es, and Stevens, *Rec. trav. chim.* **84**, 594 (1965).

[153] Stevens and van Es, *Rec. trav. chim.* **83**, 863 (1964).

1-16 Formylation with carbon monoxide and HCl. The Gatterman-Koch reaction

$$\mathrm{ArH + CO + HCl \xrightarrow[CuCl]{AlCl_3} ArCHO}$$

Certain aromatic compounds can be formylated with a mixture of CO and HCl in the presence of $AlCl_3$. The method is known as the *Gatterman-Koch reaction.*[154] The mixture of CO and HCl apparently behaves as if it were formyl chloride. The reaction has been largely limited to benzene and alkylbenzenes. It fails for phenols, phenolic ethers, and rings which contain meta-directing substituents. Substitution is largely para. An easy way to prepare the reagent mixture is to drop chlorosulfuric acid, HSO_3Cl, on formic acid, which generates CO, HCl, and H_2SO_4. Cuprous chloride is necessary if the reaction is to be carried out at atmospheric pressure. Without it, pressures of 100 to 250 atm are required. The mechanism has not been extensively investigated, but it is probable that the attacking species is the ion pair $HCO^+ \quad AlCl_4^-$, formed by transfer of a proton from the initially formed $H^+AlCl_4^-$ (itself formed by reaction between HCl and $AlCl_3$) to the carbon monoxide.[150] The function of the cuprous chloride is to coordinate with the CO, providing a higher local concentration of it. At high pressures the concentration is high enough to make the CuCl unnecessary.

OS **II**, 583.

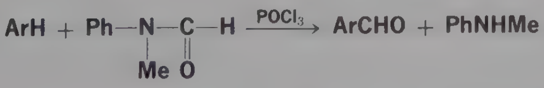
1-17 Formylation with HCN and HCl. The Gatterman reaction

$$\mathrm{ArH + HCN + HCl \xrightarrow{ZnCl_2} ArCH{=}NH_2^+ \quad Cl^- \xrightarrow{H_2O} ArCHO}$$

Formylation with HCN and HCl is called the *Gatterman reaction.*[155] In contrast to reaction **1-16**, this method may be successfully applied to phenols and their ethers, and to many heterocyclic compounds. However, it cannot be applied to aromatic amines. The use of HCN can be avoided by the substitution of $Zn(CN)_2$ and HCl for HCN and $ZnCl_2$. The mechanism has not been investigated very much, but there is an initial nitrogen-containing product which is normally not isolated but is hydrolyzed to aldehyde. The above structure is presumed for this product. The Gatterman reaction may be regarded as a special case of reaction **1-27.**

OS **III**, 549.

1-18 Formylation with disubstituted formamides



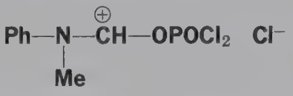
$$\mathrm{ArH + Ph{-}\underset{Me}{\underset{|}{N}}{-}\underset{O}{\underset{\|}{C}}{-}H \xrightarrow{POCl_3} ArCHO + PhNHMe}$$

The reaction with disubstituted formamides and phosphorus oxychloride, which is called the *Vilsmeier* or the *Vilsmeier-Haack reaction,* is today the most common method for the formylation of aromatic rings.[156] However, it is applicable only to active substrates, such as amines and phenols. Aromatic hydrocarbons and heterocycles can also be formylated, but only if they are much more active than benzene (e.g., azulenes, ferrocenes). Although N-phenyl-N-methylformamide is a common reagent, other arylalkyl amides and dialkyl amides are also used. $CoCl_2$ has been used in place of $POCl_3$. The reaction has also been carried out with other amides to give ketones (actually an example of reaction **1-14**) but not often.

---

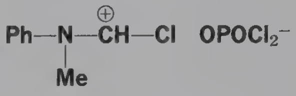
[154] For a review, see Crounse, *Org. Reactions* **5,** 290–300 (1949).

[155] For a review, see Truce, *Org. Reactions* **9,** 37–72 (1957).



$\mathrm{Ph{-}\underset{\displaystyle Me}{N}{-}\overset{\oplus}{C}H{-}OPOCl_2\quad Cl^-}$

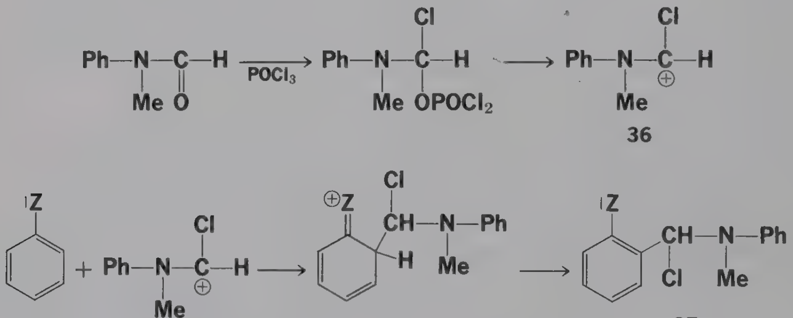
35



$\mathrm{Ph{-}\underset{\displaystyle Me}{N}{-}\overset{\oplus}{C}H{-}Cl\quad OPOCl_2^-}$

36

Two structures have been proposed for the actual attacking entity, **35** and **36**. Nuclear magnetic resonance and other evidence support **36**,[157] with the following probable mechanism:



36

37

37 is unstable and easily hydrolyzes to the product.

OS **I**, 217; **III**, 98; **IV**, 331, 539, 831, 915.

1-19 Formylation with formyl fluoride

$$\mathrm{ArH + FCHO \xrightarrow{BF_3} ArCHO}$$

In contrast to formyl chloride, formyl fluoride is stable enough to be used to formylate aromatic rings, with BF_3 as catalyst.[158] The scope of the reaction has not been extensively investigated. It has been successful for benzene, alkylbenzenes, chloro- and fluorobenzene, and naphthalene. The mechanism is presumably the same as that of reaction **1-14.**

[156] For reviews, see de Maheas, *Bull. Soc. chim. France* **1962**, 1989–1999; and Minkin and Dorofeenko, *Russ. Chem. Rev.* **29**, 599 (1960).

[157] Arnold and Holý, *Collection Czech. Chem. Commun.* **27**, 2886 (1962); Martin and Martin, *Bull. Soc. chim. France* **1963**, 1637.

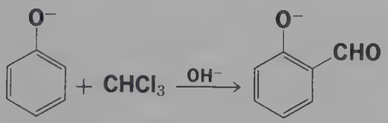
[158] Olah and Kuhn, *J. Am. Chem. Soc.* **82**, 2380 (1960).

1-20 Formylation with dichloromethyl methyl ether

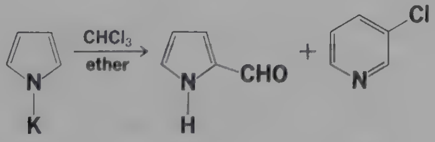
$$\mathrm{ArH} + \mathrm{Cl_2CHOMe} \xrightarrow{\mathrm{AlCl_3}} \mathrm{ArCHO}$$

Dichloromethyl methyl ether can formylate aromatic rings with Friedel-Crafts catalysts.[159] ArCHClOMe is probably an intermediate. Orthoformates have also been used, in a similar reaction. When phenoxymagnesium halides (ArOMgX) are formylated with orthoformates, only ortho products are obtained, in yields of 10 to 50%.[160]

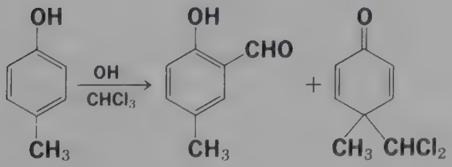
1-21 Formylation with chloroform. The Reimer-Tiemann reaction



In the *Reimer-Tiemann reaction* chloroform and hydroxide ion are used to formylate aromatic rings.[161] The method is useful only for phenols and certain heterocyclic compounds such as pyrroles and indoles. Among the formylation methods (reactions **1-16** to **1-21**) it is the only method conducted in basic solution. The incoming group is directed ortho, unless both ortho positions are filled, in which case the attack is para. Certain substrates have been shown to give abnormal products instead of or in addition to the normal ones. For example, **38** gave **40** as well as **39**, and **41** gave not only **42**, but also **43**:



38 **39** **40**



41 **42** **43**

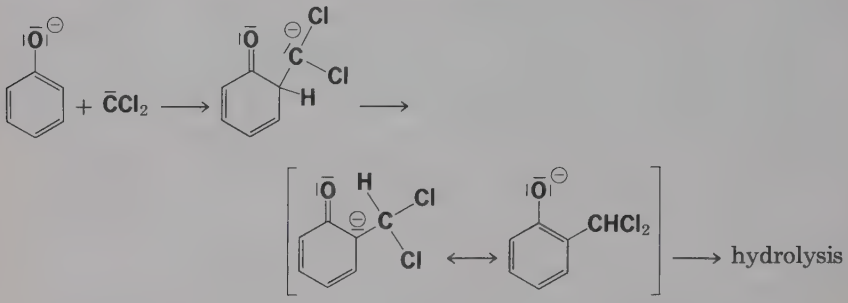
From the nature of the reagents and from the kind of abnormal products obtained, it is clear that the attacking entity in this reaction is dichlorocarbene, CCl_2: This is known to be produced by treatment of chloroform with bases (p. 163); it is an electrophilic reagent; and it is known to give ring expansion of aromatic rings (see reaction **5-37**, p. 643), accounting for products like **40**. The production of **43** may be explained by the great reactivity of carbenes. The mechanism of the normal reaction is thus something like this:[162]

---

[159] Rieche, Gross, and Höft, *Chem. Ber.* **93**, 88 (1960).

[160] Casnati, Crisafulli, and Ricca, *Tetrahedron Letters* **1965**, 243.

[161] For a review, see Wynberg, *Chem. Rev.* **60**, 169–184 (1960).



A method closely related to the Reimer-Tiemann reaction is the *Duff reaction,* in which hexamethylenetetramine [$(CH_2)_6N_4$] is used instead of chloroform. This reaction can be applied only to phenols and amines, and the yields are low.

OS **III**, 463; **IV**, 866.

Reactions **1-22** and **1-23** are direct carboxylations of aromatic rings.[163]

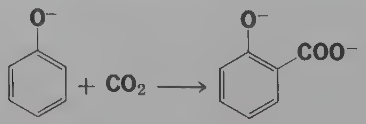
1-22 Carboxylation with carbonyl halides

$$\mathrm{ArH} + \mathrm{COCl_2} \xrightarrow{\mathrm{AlCl_3}} \mathrm{ArCOOH}$$

Phosgene, in the presence of Friedel-Crafts catalysts, may carboxylate the ring. This process is analogous to reaction **1-14**, but the ArCOCl initially produced hydrolyzes to the carboxylic acid. However, in most cases the reaction does not take this course, but instead the ArCOCl attacks another ring to give a ketone ArCOAr. A number of other reagents have been used to get around this difficulty, among them oxalyl chloride, urea hydrochloride, and carbamyl chloride, H_2NCOCl. The latter reaction is called the *Gatterman amide synthesis.* Among compounds carboxylated by one or another of these reagents are benzene, alkylbenzenes, and fused ring systems.

OS **44**, 69.

1-23 Carboxylation with carbon dioxide. The Kolbe-Schmitt reaction

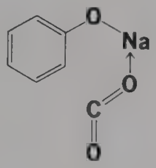


---

[162] Robinson, *J. Chem. Soc.* **1961**, 1663; Hine and van der Veen, *J. Am. Chem. Soc.* **81**, 6446 (1959).

[163] For a review, see Olah and Olah, in Olah, Ref. 136, vol. 3, pp. 1257–1273.

Phenolates may be carboxylated, mostly in the ortho position, by carbon dioxide. The process is called the *Kolbe-Schmitt reaction.*[164] The mechanism is not clearly understood, but apparently there is some kind of a complex formed between the reactants[165]

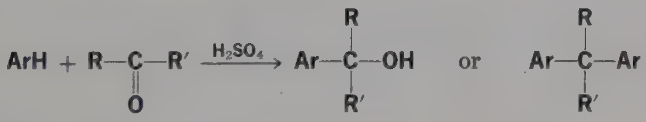


making the carbon of the CO_2 more positive and putting it in a good position to attack the ring. Carbon tetrachloride may be used instead of CO_2, under Reimer-Tiemann (reaction **1-21**) conditions.

OS **II**, 557.

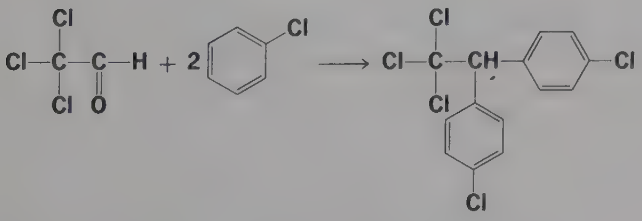
Reactions **1-24** to **1-26** involve the introduction of a CH_2Z group, where Z is halogen, hydroxy, or amino. They are all Friedel-Crafts reactions of aldehydes and ketones and, with respect to the carbonyl compound, additions to the C=O double bond. They follow mechanisms discussed in Chapter 15.

1-24 Hydroxyalkylation



$$\mathrm{ArH} + \mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R'} \xrightarrow{H_2SO_4} \mathrm{Ar{-}\overset{\displaystyle R}{\overset{|}{\underset{\underset{\displaystyle R'}{|}}{C}}}{-}OH} \quad \text{or} \quad \mathrm{Ar{-}\overset{\displaystyle R}{\overset{|}{\underset{\underset{\displaystyle R'}{|}}{C}}}{-}Ar}$$

The condensation of aromatic rings with aldehydes or ketones is called *hydroxyalkylation.*[166] The reaction is not generally useful as a method for the preparation of alcohols, although it has been used for that purpose, largely with ketones as reagents. More often, the alcohol initially produced reacts with another molecule of aromatic compound to give diarylation. For this the reaction is quite useful, an example being the preparation of DDT:



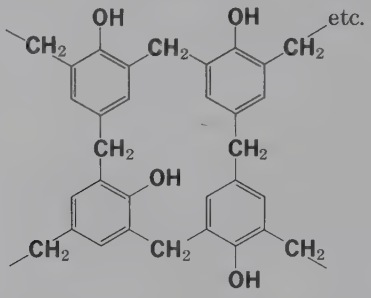
---

[164] For a review, see Lindsey and Jeskey, *Chem. Rev.* **57**, 583–620 (1957).

[165] Hales, Jones, and Lindsey, *J. Chem. Soc.* **1954**, 3145.

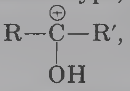
[166] For a review, see Hofmann and Schriesheim, in Olah, Ref. 136, vol. 2, pp. 597–640.

The diarylation reaction is especially common with phenols. It is normally carried out in alkaline solution, on the phenolate ion.[167] The hydroxymethylation of phenols with formaldehyde is called the *Lederer-Manasse reaction.* This reaction must be carefully controlled, since it is possible for the para and both ortho positions to be substituted and then for each of these to be rearylated, so that a polymeric structure (**44**) is produced.

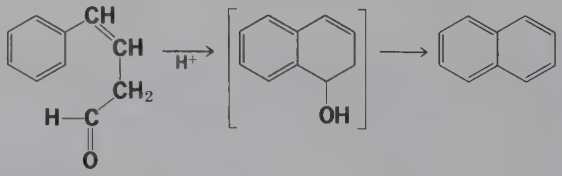


44

However, such polymers, which are of the Bakelite type, are quite useful.

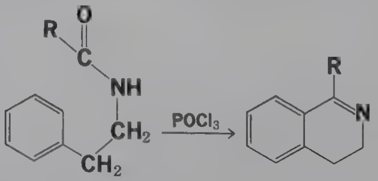
The attacking species is the carbonium ion,  $R-\overset{\oplus}{\underset{OH}{C}}-R'$, formed from the aldehyde or ketone and the acid catalyst, except when the reaction is carried out in basic solution.

An important use of this reaction is for ring closure. However, in these cases the hydroxyalkyl group which is first formed usually undergoes dehydration, since the new double bond is conjugated with an aromatic ring. An example is



Among the important special cases of this reaction may be mentioned the following:

1. *The Bischler-Napieralski reaction.*[168] In this reaction amides of the type **45** are cyclized with phosphorus oxychloride:



45

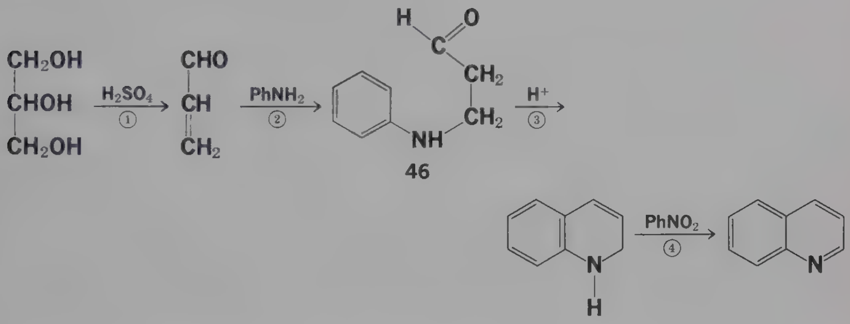
---

[167] For a review, see Schnell and Krimm, *Angew. Chem. Intern. Ed. Engl.* **2,** 373–379 (1963).

[168] For a review, see Whaley and Govindachari, *Org. Reactions* **6,** 74–150 (1951).

If the starting compound contains a hydroxyl group in the α position, then an additional dehydration takes place, and the product is an isoquinoline. The Bischler-Napieralski reaction was used in the total synthesis of papaverine[169] and of reserpine.[170]

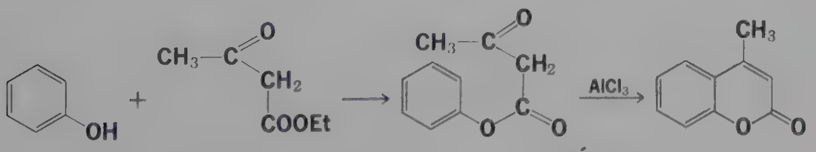
2. *The third step of the Skraup synthesis.*[171] In the Skraup synthesis a primary aromatic amine is treated with glycerol, sulfuric acid, and an aromatic nitro compound (usually nitrobenzene) to give a quinoline. The reaction has four steps, as shown:



46

The third step is the Friedel-Crafts ring closure. The first step is a dehydration reaction **7-1**, p. 753), the second a Michael reaction (**5-9**, p. 589), and the fourth an oxidative aromatization (reaction **9-1**, p. 859) in which nitrobenzene is the oxidizing agent. Intermediates of the type **46** have been isolated from the reaction mixture[172] and have been shown to give quinolines under these conditions.[173] Since in the first step glycerol is dehydrated to acrolein, it might be expected that other α,β-unsaturated aldehydes and ketones also give the reaction. This is true, the reaction being called the *Doebner-Miller reaction.*

3. The *Pechmann (or von Pechmann) reaction.*[174] In this reaction phenols are condensed with β-keto esters to give coumarins. The first step is a transesterification (reaction **0-26**, p. 322) and the second a Friedel-Crafts ring closure:



OS **I,** 360, 478; **II,** 62, 194; **III,** 281, 300, 326, 329, 568, 580, 581; **IV,** 590; **40,** 43; **42,** 57. Also see OS **I,** 54, 214.

---

[169] Pictet and Gams, *Ber.* **42,** 2943 (1909).

[170] Woodward, Bader, Bickel, Frey, and Kierstead, *Tetrahedron* **2,** 1 (1958).

[171] For a review, see Manske and Kulka, *Org. Reactions* **7,** 59–98 (1953).

[172] Badger, Crocker, Ennis, Gayler, Matthews, Raper, Samuel, and Spotswood, *Australian J. Chem.* **16,** 814 (1963); Badger, Crocker, and Ennis, *Australian J. Chem.* **16,** 840 (1963).

[173] Badger, Ennis, and Matthews, *Australian J. Chem.* **16,** 828 (1963).

[174] For a review, see Sethna and Phadke, *Org. Reactions* **7,** 1–58 (1953).

1-25 Haloalkylation[175]

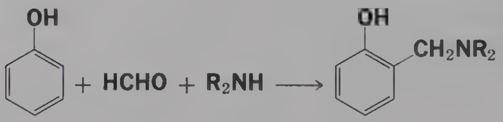
$$ArH + HCHO + HCl \xrightarrow{ZnCl_2} ArCH_2Cl$$

When certain aromatic compounds are treated with formaldehyde and HCl, the CH_2Cl group is introduced into the ring, in a reaction called *chloromethylation*. The reaction has also been carried out with other aldehydes and with HBr and HI. The more general term *haloalkylation* covers these cases. The reaction is successful for benzene, and alkyl, alkoxy, and halobenzenes. It is greatly hindered by meta-directing groups, which reduce yields or completely prevent the reaction. Amines and phenols are too reactive and usually give polymers, unless deactivating groups are also present, but phenolic ethers and esters successfully undergo the reaction. Zinc chloride is the most common catalyst, but other Friedel-Crafts catalysts are also employed. As with reaction **1-24,** and for the same reason, an important side product is the diaryl compound Ar_2CH_2 (from formaldehyde).

Apparently the initial step involves reaction of the aromatic compound with the aldehyde to form the hydroxyalkyl compound, exactly as in reaction **1-24,** and then the HCl converts this to the chloroalkyl compound.[176]

OS **III,** 195, 197, 468, 557; **IV,** 980.

1-26 Aminoalkylation



Phenols may be aminomethylated by treatment with formaldehyde and a secondary amine. The ortho position is preferred, but all three ortho and para positions may be substituted. Aminomethylation is a special case of the Mannich reaction (**6-17,** p. 670).

OS **I,** 381; **IV,** 626; **40,** 31.

1-27 Acylation with nitriles. The Hoesch reaction

$$ArH + RCN \xrightarrow[ZnCl_2]{HCl} ArCOR$$

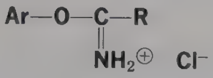
Friedel-Crafts acylation with nitriles and HCl is called the *Hoesch* or the *Houben-Hoesch* reaction.[177] In most cases, a Lewis acid is necessary, zinc chloride being the most common. The reaction is useful only with phenols, phenolic ethers, and some reactive heterocyclic compounds, e.g., pyrrole. Many nitriles have been used. Even aryl nitriles give good yields if they are first treated with HCl and $ZnCl_2$, and then the phenol added at 0°.[178] In fact, this procedure increases yields with any nitrile. Compounds of the type **47** are obtained as side products, resulting from attack at the oxygen of

---

[175] For reviews, see Olah and Tolgyesi, in Olah, Ref. 136, vol. 2, pp. 659–784; and Fuson and McKeever, *Org. Reactions* **1,** 63–90 (1942).

[176] Ziegler, Hontschik, and Milowiz, *Monatsh. Chem.* **78,** 334 (1947); Ziegler, *Monatsh. Chem.* **79,** 142 (1948).

[177] For reviews, see Spoerri and DuBois, *Org. Reactions* **5,** 387–412 (1949); Zil'berman, *Russ. Chem. Rev.* **31,** 615–633 (1962); and Ruske, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 383–497, Interscience Publishers, Inc., New York, 1964.

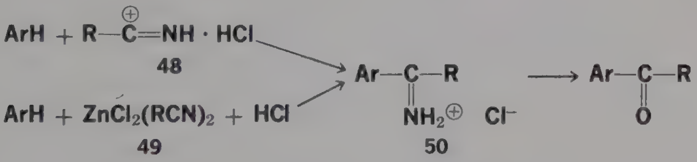


$$Ar{-}O{-}\underset{\underset{NH_2^{\oplus}}{\|}}{C}{-}R \quad Cl^-$$

47

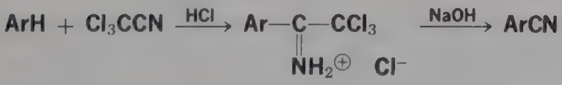
the phenol. If thiocyanates, RSCN, are used, thiol esters, ArCOSR, may be obtained. The Gatterman reaction (**1-17**) is a special case of the Houben-Hoesch synthesis.

The reaction mechanism is complex and not completely settled.[179] The first stage consists of an attack on the substrate by a species containing the nitrile and HCl (and the Lewis acid, if present), to give an imine salt (**50**). Among the possible attacking species are **48** and **49**. In the second stage, the salts are hydrolyzed to the products:



OS **II**, 522.

1-28 Direct cyanogenation



$$ArH + Cl_3CCN \xrightarrow{HCl} Ar{-}\underset{\underset{NH_2^{\oplus}}{\|}}{C}{-}CCl_3 \quad Cl^- \xrightarrow{NaOH} ArCN$$

Aromatic hydrocarbons (including benzene), phenols, and phenolic ethers may be cyanogenated with trichloroacetonitrile, BrCN, or mercury fulminate, $Hg(ONC)_2$.[180] In the case of Cl_3CCN, the actual attacking entity is probably $Cl_3C{-}\overset{\oplus}{C}{=}NH$, formed by addition of a proton to the cyano nitrogen. The cyano group has also been introduced electrolytically, by applying a potential to a mixture of the aromatic compound, HCN, and NaCN, in methanol.[181] Ferrocenes have been cyanogenated by HCN and $FeCl_3$, but this is nucleophilic aromatic substitution, since the $FeCl_3$ oxidizes the ferrocene to a positive ion which is attacked by CN^-.[182]

---

[178] Zil'berman and Rybakova, *J. Gen. Chem. USSR* **30**, 1972 (1960).

[179] For discussions, see Ref. 177 and Jeffery and Satchell, *J. Chem. Soc.* (*B*) **1966**, 579.

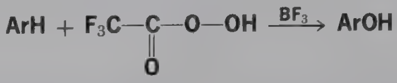
[180] Olah, in Olah, Ref. 136, vol. 1, pp. 119–120.

[181] Koyama, Susuki, and Tsutsumi, *Tetrahedron Letters* **1965**, 627; Parker and Burgert, *Tetrahedron Letters* **1965**, 4065.

OS **III**, 293.

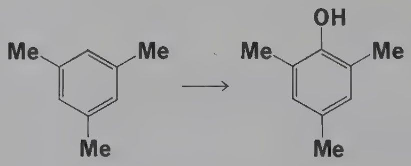
F. Oxygen electrophiles. Oxygen electrophiles are very uncommon, since oxygen does not bear a positive charge very well. However, there are two reactions which may be mentioned.

1-29 Direct hydroxylation

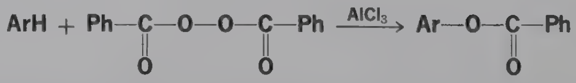


$$ArH + F_3C{-}\underset{\underset{O}{\|}}{C}{-}O{-}OH \xrightarrow{BF_3} ArOH$$

There have been only a few reports of direct hydroxylation by an electrophilic process (see, however, reactions **3-20**, p. 511, and **4-5**, p. 538).[183] In general, poor results are obtained, in part because the introduction of an OH group activates the ring to further attack. Quinone formation is common. However, alkyl-substituted benzenes such as mesitylene or durene may be hydroxylated in good yield with trifluoroperacetic acid and boron trifluoride.[184] In the case of mesitylene, the product is not subject to further attack:



1-30 Direct introduction of an acyloxy group



$$ArH + Ph{-}\underset{\underset{O}{\|}}{C}{-}O{-}O{-}\underset{\underset{O}{\|}}{C}{-}Ph \xrightarrow{AlCl_3} Ar{-}O{-}\underset{\underset{O}{\|}}{C}{-}Ph$$

An acyloxy group may be introduced into an aromatic ring by treatment with a diacyl peroxide and a Friedel-Crafts catalyst.[185] Although peroxides often react by free-radical mechanisms, this is not the case here, as shown by three facts: (1) a Friedel-Crafts catalyst is required; (2) little or no CO_2 is found (a normal product from the PhCOO· radical); (3) when the reaction was performed with benzoyl peroxide labeled in the carbonyl oxygen, all of the ester product was labeled in the carbonyl oxygen.[186] If PhCOO· were an intermediate, then both oxygens of the product should be labeled. The labeling evidence also rules out a free ion $PhCOO^+$ formed by a Lewis acid-base reaction: $PhCOOOCOPh + AlCl_3 \longrightarrow PhCOO^+ + Cl_3AlOCOPh^-$; hence it is likely that the attack is by a complex between the reagent and the catalyst.

---

[182] Nesmeyanov, Perevalova, Yur'eva, and Grandberg, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1962**, 1681; Nesmeyanov, Perevalova, and Yur'eva, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1965**, 875.

[183] For a review of electrophilic hydroxylation, see Norman and Taylor, Ref. 1, pp. 110–116.

[184] Hart and Buehler, *J. Org. Chem.* **29**, 2397 (1964). For other hydroxylations, see Chambers, Goggin, and Musgrave, *J. Chem. Soc.* **1959**, 1804; Hamilton and Friedman, *J. Am. Chem. Soc.* **85**, 1008 (1963); Kovacic and Morneweck, *J. Am. Chem. Soc.* **87**, 1566 (1965); and Kovacic and Kurz, *J. Am. Chem. Soc.* **87**, 4811 (1965); *J. Org. Chem.* **31**, 2011, 2459 (1966).

[185] Reynhart, *Rec. trav. chim.* **46**, 54 (1927).

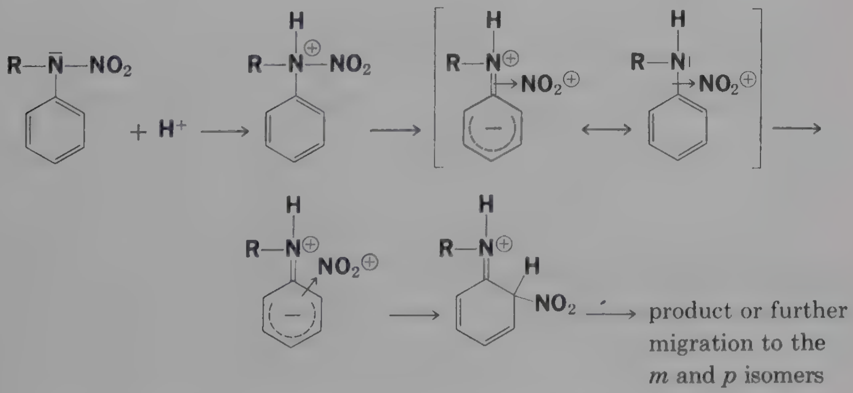
[186] Denney and Weiss, *Chem. Ind.* (*London*) **1962**, 818.

Arylsulfonyl peroxides similarly react with aromatic compounds to give sulfonic esters:[187]

$$ArH + Ar'{-}SO_2{-}O{-}O{-}SO_2{-}Ar' \longrightarrow Ar{-}O{-}SO_2{-}Ar'$$

G. Metal electrophiles. Reactions in which a metal replaces the hydrogen of an aromatic ring are considered along with their aliphatic counterparts in Chapter 12 (reactions **2-12,** p. 468, and **2-13,** p. 470).

Hydrogen as the Leaving Group in Rearrangement Reactions. In these reactions a group is first detached from a *side chain* and then attacks the ring, but in other respects they resemble the reactions already treated in this chapter.[188] Since a group moves from one position to another in a molecule, these are rearrangements. In all these reactions the question arises as to whether the group which cleaves from a given molecule attacks the same molecule or another one, that is, is the reaction intramolecular or intermolecular? For those that are intermolecular the mechanism is the same as ordinary aromatic substitution, but for intramolecular cases, the migrating group could never be completely free, or else it would be able to attack another molecule. Dewar has proposed a mechanism for the intramolecular cases, in which the migrating group is always held to the original ring by formation of a π-complex.[189] This may be illustrated for the case of reaction **1-33:**



---

[187] Crovatt and McKee, *J. Org. Chem.* **24,** 2031 (1959); Haszeldine, Heslop, and Lethbridge, *J. Chem. Soc.* **1964,** 4901; Dannley and Corbett, *J. Org. Chem.* **31,** 153 (1966).

[188] For a review of these rearrangements, see Dewar, in Mayo, "Molecular Rearrangements," vol. 1, pp. 295–299, 306–323, Interscience Publishers, Inc., New York, 1963.

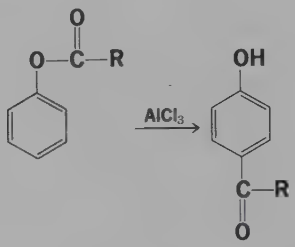
[189] Dewar, in "Theoretical Organic Chemistry, The Kekulé Symposium," pp. 179–208, Butterworth Scientific Publications, London, 1959.

According to this mechanism, ortho rearrangement should predominate, since the fairly stable ortho complex should have little reason to go on the meta. One of the methods used to tell the difference between the inter- and intramolecular processes is that ortho rearrangement does predominate in the intramolecular cases.

The Claisen (**8-25**, p. 830) and benzidine (**8-24**, p. 828) rearrangements, which superficially resemble those in this section, have different mechanisms and are treated in Chapter 18.

A. Groups cleaving from oxygen

1-31 The Fries rearrangement



Phenolic esters may be rearranged by heating with Friedel-Crafts catalysts. The reaction is known as the *Fries rearrangement.*[190] Both *ortho-* and *para*-acylphenols may be produced, and it is often possible to select conditions so that either one predominates. Rearrangement has also been found to give meta products.[191] R may be aliphatic or aromatic. Any meta-directing substituent on the ring interferes with the reaction, as might be expected for a Friedel-Crafts process.

The exact mechanism has still not been completely worked out. Apparently it is sometimes inter- and sometimes intramolecular. One way to decide between the two alternatives is to run the reaction of the phenolic ester in the presence of another aromatic compound, say, toluene. If some of the toluene is acylated, then the reaction must be, at least in part, intermolecular. If the toluene is not acylated, the presumption is that the reaction is intramolecular, although this is not certain, for it may be that the toluene is not attacked because it is less active than the other. Just such experiments were carried out,[192] and it was found that the use of **51** resulted in acylated toluene, but **52** did not. In either case there is an initial complex (**53**) formed between the substrate and the catalyst. There is evidence that both a mono- and a di-$AlCl_3$ complex are formed.[193]

The Fries rearrangement has also been carried out without a catalyst, but

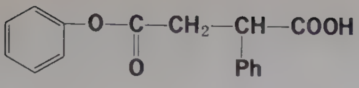
---

[190] For reviews, see Blatt, *Org. Reactions* **1**, 342–369 (1942); and Gerecs, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 499–533, Interscience Publishers, Inc., New York, 1964.

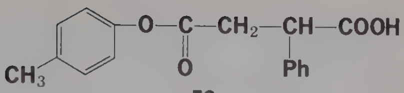
[191] Da Re and Cimatoribus, *J. Org. Chem.* **26**, 3650 (1961).

[192] El-Abbady, Baddar, and Labib, *J. Chem. Soc.* **1961**, 1083.

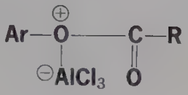
[193] Cullinane, Woolhouse, and Edwards, *J. Chem. Soc.* **1961**, 3842; Cullinane and Bailey-Wood, *Rec. trav. chim.* **78**, 440 (1959).



51



52



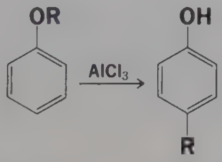
$$Ar-\overset{\oplus}{\underset{\ominus AlCl_3}{O}}-\underset{O}{\overset{\|}{C}}-R$$

53

in the presence of ultraviolet light. This is predominantly an intramolecular free-radical process, in which the attacking entity is RCOO·.[194]

OS **II**, 543; **III**, 280, 282.

1-32 Rearrangement of phenolic ethers



This reaction bears the same relationship to reaction **1-31** that reaction **1-12** bears to **1-14**. Isomerization of the R group is usually found when that is possible. Both phenyl *n*-butyl ether and phenyl *sec*-butyl ether give *p*-*sec*-butylphenol.[195] The mechanism is probably similar to that of reaction **1-31**. Evidence has been found for both inter- and intramolecular processes. The fact that dialkylphenols were isolated in the above case shows that at least some intermolecular processes were occurring. Evidence for intramolecular reaction is that conversion of optically active *p*-tolyl *sec*-butyl ether to 2-*sec*-butyl-4-methylphenol proceeded with some retention of configuration,[196] and that rearrangement of *p*-tolyl benzyl ether (with $SbCl_3$) took place with only ortho migration.[197] In at least some cases the reaction can proceed without a catalyst. For example, simple heating at 250° of phenyl benzyl ether gave *ortho*- and *para*-benzylphenol.[198] The fact that phenol and toluene are also obtained shows that the thermal reaction is intermolecular. It is probably a free-radical reaction.

B. Groups cleaving from nitrogen.[199] It has been shown that $Ph\overset{\oplus}{N}H_2D$ rearranges to *ortho*- and *para*-deuterioaniline.[200] The migration of OH, formally similar to reactions **1-33** to **1-37**, is a nucleophilic substitution and is treated in Chapter 13 (reaction **3-28**, p. 519).

---

[194] Kobsa, *J. Org. Chem.* **27**, 2293 (1962); Anderson and Reese, *J. Chem. Soc.* **1963**, 1781; Taub, Kuo, Slates, and Wendler, *Tetrahedron* **19**, 1 (1963); Finnegan and Matice, *Tetrahedron* **21**, 1015 (1965).

[195] Dewar and Puttnam, *J. Chem. Soc.* **1959**, 4080, 4086.

[196] Sprung and Wallis, *J. Am. Chem. Soc.* **56**, 1715 (1934).

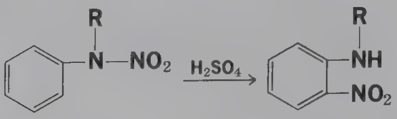
[197] Cullinane, Woolhouse, and Carter, *J. Chem. Soc.* **1962**, 2995.

[198] Elkobaisi and Hickinbottom, *J. Chem. Soc.* **1959**, 1873, **1960**, 1286.

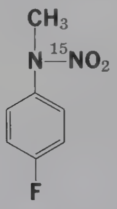
[199] For a review, see Hughes and Ingold, *Quart. Rev.* (*London*) **6**, 34–62 (1952).

[200] Okazaki and Okumura, *Bull. Chem. Soc. Japan* **34**, 989 (1961).

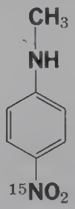
1-33 Migration of the nitro group



N-Nitro aromatic amines rearrange on treatment with acids to give *ortho*- and *para*-nitroamines, with the ortho compounds predominating. Aside from this indication of an intramolecular process, it was shown that rearrangement of N-nitroaniline, N-nitro-1-naphthylamine, and N-nitro-N-methyl-1-naphthylamine, in the presence of $K^{15}NO_3$ gave products containing no ^{15}N,[201] and that rearrangement of a mixture of $PhNH^{15}NO_2$ and unlabeled p-$MeC_6H_4NHNO_2$ gave 2-nitro-4-methylaniline containing no ^{15}N.[202] On the other hand, rearrangement of **54** in the presence of unlabeled $PhNMeNO_2$ gave labeled **55**, which did not arise by displacement of F.[203] As has been indicated by the examples given, R may be hydrogen or alkyl.



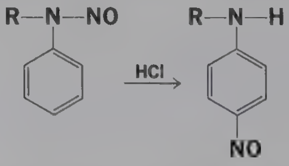
54



55

The actual electrophile is in doubt. Mechanisms as disparate as a cyclic attack (attack by the oxygen of the nitro group at the ortho position before the group cleaves)[204] and an actual cleavage into a radical and an ion-radical ($Ar\overset{\oplus}{N}HMeNO_2 \longrightarrow Ar\overset{\oplus}{N}HMe\cdot + NO_2\cdot$)[205] have been proposed. Evidence for the latter view is that both N-methylaniline and nitrous acid are produced in sizable and comparable amounts from N-nitro-N-methylaniline, in addition to the normal product, p-nitro-N-methylaniline. See also page 427.

1-34 Migration of the nitroso group. The Fischer-Hepp rearrangement



---

[201] Brownstein, Bunton, and Hughes, *J. Chem. Soc.* **1958**, 4354; Banthorpe, Thomas, and Williams, *J. Chem. Soc.* **1965**, 6135.

[202] Geller and Dubrova, *J. Gen. Chem. USSR* **30**, 2627 (1960).

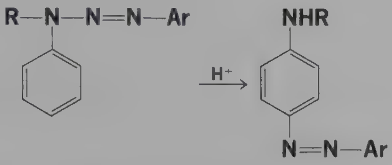
[203] White and Golden, *Chem. Ind.* (*London*) **1962**, 138.

[204] Banthorpe, Hughes, and Williams, *J. Chem. Soc.* **1964**, 5349; Banthorpe and Thomas, *J. Chem. Soc.* **1965**, 7149, 7158. Also see Ref. 201.

[205] White, Lazdins, and White, *J. Am. Chem. Soc.* **86**, 1517 (1964).

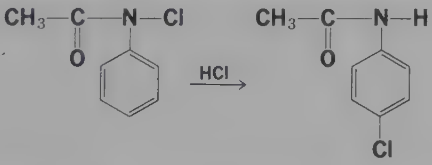
The migration of a nitroso group, formally similar to reaction **1-33**, is important because *p*-nitroso secondary aromatic amines cannot be prepared by direct C-nitrosation of secondary aromatic amines (see reaction **2-35**, p. 486). The reaction is known as the *Fischer-Hepp rearrangement.* The para product is predominantly formed, indicating an intermolecular process. The attacking entity is probably NO^+ or a derivative of it, perhaps NOCl.

1-35 Migration of an arylazo group



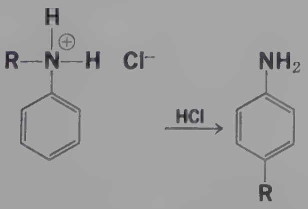
Rearrangement of aryl triazenes is used to prepare azo derivatives of primary and secondary aromatic amines.[206] These are first diazotized at the amino group (see reaction **1-4**) to give triazenes, which are then rearranged. The rearrangement always gives the para isomer unless that position is occupied. The reaction is intermolecular, with the migrating species probably being ArN_2^+.

1-36 Migration of halogen. The Orton rearrangement



Migration of a halogen from a nitrogen side chain to the ring is called the *Orton rearrangement.*[207] The reaction has been carried out with N-chloro- and N-bromoamines, and less often with N-iodo compounds. The amine must be acylated, except that $PhNCl_2$ gives 2,4-dichloroaniline. The reaction is usually performed in water or acetic acid. There is much evidence (cross-halogenation, labeling, etc.) that this is an intermolecular process. Chlorine has been isolated from the reaction mixture, so that it is likely that first the HCl reacts with the starting material to give $ArNHCOCH_3$ and Cl_2, and that the chlorine then halogenates the ring as in reaction **1-11**.

1-37 Migration of an alkyl group



---

[206] For a review, see Zollinger, "Azo and Diazo Chemistry," pp. 182–187, Interscience Publishers, Inc., New York, 1961.

[207] For a review, see de la Mare and Ridd, Ref. 1, pp. 151–155.

When salts of arylalkylamines are heated with HCl, migration occurs. This is called the *Hofmann-Martius reaction.* It is an intermolecular reaction, since crossing is found. For example, methylanilinium bromide gave not only the normal products, *ortho-* and *para-*toluidine, but also aniline and di- and trimethylanilines.[208] As would be expected for an intermolecular process, there is isomerization when R is primary.

With primary R, the reaction probably goes through the alkyl halide formed initially in a nucleophilic substitution reaction:

$$R\overset{\oplus}{N}H_2Ar + Cl^- \longrightarrow RCl + ArNH_2$$

Evidence for this view is that alkyl halides have been isolated from the reaction mixture, and that Br^-, Cl^-, and I^- gave different ortho-para ratios, indicating that the halogen is involved in the reaction.[208] The attack of the alkyl halide is, as in reaction **1-12,** probably through the carbonium ion. The alkyl halides isolated are unrearranged, though alkyl groups in the ring are rearranged. When R is secondary or tertiary, carbonium ions may be directly formed so that the reaction does not go through the alkyl halides.[209]

It is also possible to carry out the reaction by heating the amine (not the salt) at 220° with $CoCl_2$. When this is done, the reaction is called the *Reilly-Hickinbottom rearrangement.* Under these conditions primary R groups do not rearrange. However, this reaction is useless for secondary and tertiary R groups, since these groups are simply cleaved to olefins under these conditions. The mechanism of the Reilly-Hickinbottom rearrangement is obscure.

Other Leaving Groups. Three types of reaction will be considered in this section.

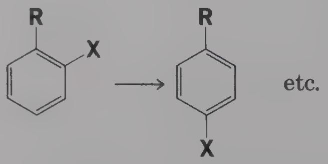
1. Reactions in which hydrogen replaces another leaving group:

$$ArX + H^+ \longrightarrow ArH$$

2. Reactions in which an electrophile other than hydrogen replaces another leaving group:

$$ArX + Y^+ \longrightarrow ArY$$

3. Reactions in which a group (other than hydrogen) migrates from one position in a ring to another:



Such migrations may be either inter- or intramolecular.

---

[208] Ogata, Tabuchi, and Yoshida, *Tetrahedron* **20,** 2717 (1964).
[209] Hart and Kosak, *J. Org. Chem.* **27,** 116 (1962).

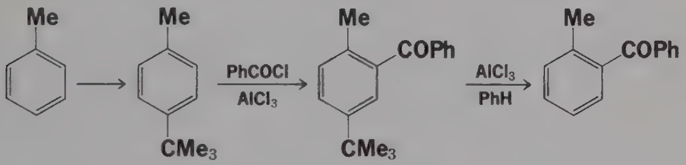
The three types will not be treated separately, but reactions will be classified on the basis of the nature of the leaving group.

A. Carbon leaving groups

1-38 Reversal of Friedel-Crafts alkylation

$$\text{ArR} + \text{H}^+ \xrightarrow{\text{AlCl}_3} \text{ArH}$$

Alkyl groups may be cleaved from aromatic rings by treatment with proton and/or Lewis acids. Tertiary R groups are the most easily cleaved; because this is true, the *tert*-butyl group is occasionally introduced into a ring, used to direct another group, and then removed. For example,[210]



Secondary R groups are harder to cleave, and primary R harder still. Because of this reaction, care must be taken when using Friedel-Crafts catalysts (Lewis or proton acids) on aromatic compounds containing alkyl groups. True cleavage, in which the R becomes an olefin, occurs only at high temperatures: above 400°.[211] At ordinary temperatures, the R group attacks another ring, so that the bulk of the product may be dealkylated, but there will be a residue of heavily alkylated material. The isomerization reaction, in which a group migrates from one position in a ring to another, or to a different ring, is therefore more important than true cleavage. This migration may be inter- or intramolecular, depending on the conditions and on the R group. The following experiments may be cited: ethylbenzene, treated with HF and BF_3, gave, almost completely, benzene and diethylbenzenes[212] (entirely intermolecular); propylbenzene, labeled in the β position, gave benzene, propylbenzene, and di- and tripropylbenzenes, but the propylbenzene recovered was partly labeled in the α position and not at all in the γ position[213] (both intra- and intermolecular); *o*-xylene treated with HBr and $AlBr_3$ gave a mixture of *ortho-* and *meta*-xylene, but no *para-*, while *p*-xylene gave *para-* and *meta*-xylene, but no *ortho-*, and no trimethyl compounds could be isolated in these experiments[214] (exclusively intramolecular rearrangement). Apparently methyl groups migrate only intramolecularly, while other groups may follow either path.[215]

---

[210] Hofman, Reiding, and Nauta, *Rec. trav. chim.* **79**, 790 (1960).

[211] Olah, in Olah, "Friedel-Crafts and Related Reactions," vol. 1, pp. 36–38, Interscience Publishers, Inc., New York, 1963.

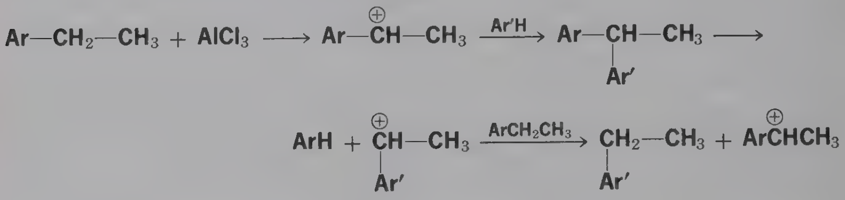
[212] McCaulay and Lien, *J. Am. Chem. Soc.* **75**, 2407 (1953).

[213] Roberts and Brandenberger, *J. Am. Chem. Soc.* **79**, 5484 (1957); Roberts and Douglass, *J. Org. Chem.* **28**, 1225 (1963).

[214] Brown and Jungk, *J. Am. Chem. Soc.* **77**, 5579 (1955); Allen and Yats, *J. Am. Chem. Soc.* **81**, 5289 (1959).

[215] Allen, Alfrey, and Yats, *J. Am. Chem. Soc.* **81**, 42 (1959); Allen, Yats, and Erley, *J. Am. Chem. Soc.* **82**, 4853 (1960); Allen, *J. Am. Chem. Soc.* **82**, 4856 (1960).

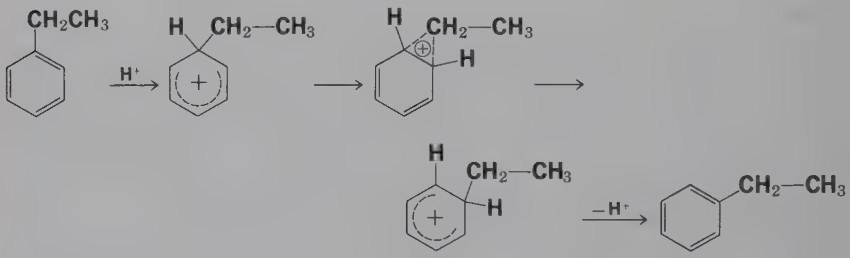
The mechanism of intermolecular rearrangement may involve free carbonium ions, but there is much evidence to show that this is not necessarily the case. For example, many of them occur without rearrangement within the alkyl group. When rearrangement does occur, it may be of the type that could not arise from a free carbonium ion. For example, *tert*-amylbenzene, when heated with $AlCl_3$, gave 65% neopentylbenzene while the latter was almost unchanged.[216] A free carbonium ion would almost certainly rearrange the other way. The following mechanism has been proposed for intermolecular rearrangement without the involvement of carbonium ions which are separated from the ring:[217]



$$\mathrm{Ar{-}CH_2{-}CH_3} + \mathrm{AlCl_3} \longrightarrow \mathrm{Ar{-}\overset{\oplus}{C}H{-}CH_3} \xrightarrow{\mathrm{Ar'H}} \mathrm{Ar{-}\underset{\displaystyle Ar'}{CH}{-}CH_3} \longrightarrow$$

$$\mathrm{ArH} + \underset{\displaystyle \mathrm{Ar'}}{\overset{\oplus}{\mathrm{C}}\mathrm{H}}\mathrm{{-}CH_3} \xrightarrow{\mathrm{ArCH_2CH_3}} \underset{\displaystyle \mathrm{Ar'}}{\mathrm{CH_2}}\mathrm{{-}CH_3} + \mathrm{Ar\overset{\oplus}{C}HCH_3}$$

Evidence for this mechanism was that optically active $PhCHDCH_3$, labeled in the ring with ^{14}C, treated with $GaBr_3$ in the presence of benzene, gave ethylbenzene containing no deuterium and two deuteriums, and that the rate of loss of radioactivity was about equal to the rate of loss of optical activity.[217] The mechanism of intramolecular rearrangement is not very clear. 1,2-Shifts of this kind have been proposed:[218]



Phenyl groups have also been found to migrate. Thus, *o*-terphenyl, heated with $AlCl_3$-H_2O, gave a mixture containing 7% *o*-, 70% *m*-, and 23% *p*-terphenyl.[219] Alkyl groups have also been replaced by groups other than hydrogen, for example, nitro groups.[220]

Alkylferrocenes also undergo disproportionation; for example, *n*-propylferrocene with $AlCl_3$ gives ferrocene and 1,1′-di-*n*-propylferrocene.[221] However, this is an entirely different process. There is no cleavage between the R group and the ring (hence rearrangement is not possible). The cleavage takes place between the ring and the central iron atom. This was shown by the fact that 1,1′,2-triethylferrocene gave only 1,1′-diethylferrocene and 1,1′,2,2′-tetraethylferrocene. Only a trace of monoethylferrocene was found. If the C—C bond between the ring and the group had broken, there would certainly have been found a substantial amount of product containing three groups in one ring and two in the other, one group in one ring and none in the other, etc.

---

[216] Roberts and Han, *Tetrahedron Letters* **1959,** No. 6, 5.
[217] Streitwieser and Reif, *J. Am. Chem. Soc.* **86,** 1988 (1964).
[218] Olah, Meyer, and Overchuk, *J. Org. Chem.* **29,** 2313 (1964).
[219] Olah and Meyer, *J. Org. Chem.* **27,** 3682 (1962).
[220] For a review, see Nightingale, *Chem. Rev.* **40,** 117 (1947).
[221] Bublitz, *Can. J. Chem.* **42,** 2381 (1964).

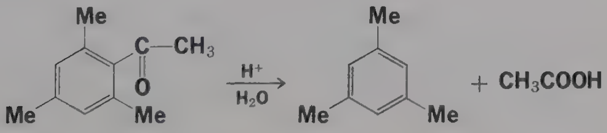
There are no OS references, but see OS **III**, 282, 653 for related reactions.

1-39 Decarbonylation of aromatic aldehydes

$$\mathrm{ArCHO} \xrightarrow{H_2SO_4} \mathrm{ArH} + \mathrm{CO}$$

The decarbonylation of aromatic aldehydes is the reverse of reaction **1-16.** It has been carried out with trialkyl and trialkoxybenzaldehydes. The attacking species is H^+, and the leaving group HCO^+, which can lose a proton to give CO or combine with OH^- from the water solvent to give formic acid.[222] Aromatic aldehydes have also been decarbonylated over Pd,[223] and with basic catalysts.[224] When basic catalysts are used, the mechanism is probably similar to the S_E1 process of reaction **1-40.**

Aromatic ketones may also be cleaved, but only when sterically hindered, e.g.,



1-40 Decarboxylation of aromatic acids

$$\mathrm{ArCOOH} \xrightarrow[\text{quinoline}]{Cu} \mathrm{ArH} + CO_2$$

Many aromatic acids may be decarboxylated by heating with copper and quinoline. Many others are decarboxylated as the ion $ArCOO^-$. When decarboxylation takes place on the acid itself, the ordinary σ-complex mechanism usually operates, with H^+ as the electrophile and $COOH^+$ as the leaving group,[225] especially when electron-donating groups are present in ortho or para positions. Evidence for this mechanism is that these reactions are first order both in H^+ and in ArCOOH, overall second order; that the reaction is subject to general acid catalysis (see p. 226);[226] that there is no $^{13}COOH$ isotope effect, indicating that cleavage does not occur in the rate-determining step;[227] and that a solvent isotope effect has been shown.[228]

---

[222] Burkett, Schubert, Schultz, Murphy, and Talbott, *J. Am. Chem. Soc.* **81,** 3923 (1959).

[223] Hawthorne and Wilt, *J. Org. Chem.* **25,** 2215 (1960).

[224] Bunnett, Miles, and Nahabedian, *J. Am. Chem. Soc.* **83,** 2512 (1961).

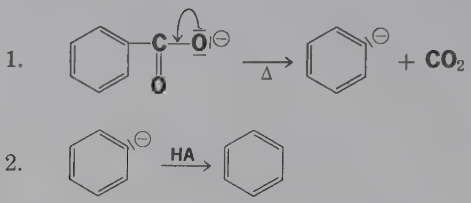
[225] For a review of decarboxylation mechanisms, see Brown, *Quart. Rev.* (*London*) **5,** 131 (1951).

[226] Willi, *Trans. Faraday Soc.* **55,** 433 (1959).

[227] Lynn and Bourns, *Chem. Ind.* (*London*) **1963,** 782.

[228] Willi, *Z. Naturforsch.* **13A,** 997 (1958).

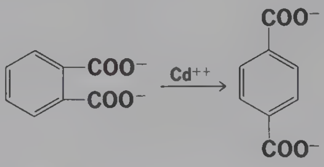
When carboxylate *ions* are decarboxylated, the mechanism is entirely different, being essentially of the S_E1 type (see p. 446):



Evidence for this mechanism is that the reaction is first order, and that electron-withdrawing groups, which would stabilize a carbanion, facilitate the reaction.

When there is a hydroxyl group para to it, the carboxyl group may be replaced by the nitroso group (the actual reacting species is $^-OC_6H_4COO^-$), so that the product is a *p*-nitrosophenol.[229] Nitrous acid is the reagent and the ordinary σ-complex mechanism operates.

Rearrangements are also known to take place. For example, when the phthalate ion (**56**) is heated with a catalytic amount of cadmium ion, the terphthalate ion (**57**) is produced:[230]



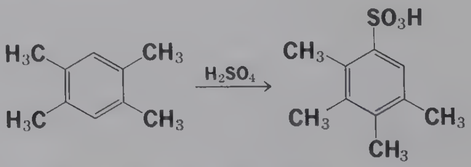
56 **57**

In a similar process, potassium benzoate, heated with cadmium salts, disproportionates to benzene and **57**. The term *Henkel reaction* is used for these rearrangements.

For aliphatic decarboxylation, see reaction **2-26** (p. 477).

OS **I**, 274, 455, 541; **II**, 100, 214, 217, 341; **III**, 267, 272, 471, 637; **IV**, 590, 628; **40**, 54, 71, 85; **46**, 101. Also see OS **I**, 56.

1-41 The Jacobsen reaction



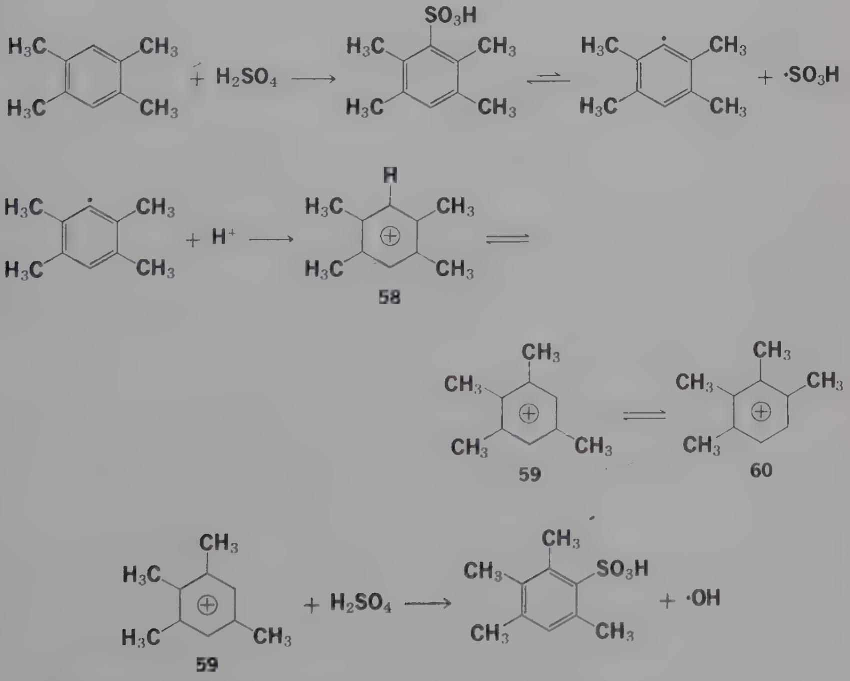
---

[229] Ibne-Rasa, *J. Am. Chem. Soc.* **84**, 4962 (1962); Tedder and Theaker, *J. Chem. Soc.* **1959**, 257.

[230] Raecke, *Angew. Chem.* **70**, 1 (1958); Riedel and Kienitz, *Angew. Chem.* **72**, 738 (1960); Ogata, Hojo, and Morikawa, *J. Org. Chem.* **25**, 2082 (1960); McNelis, *J. Org. Chem.* **30**, 1209 (1965); Ogata and Nakajima, *Tetrahedron* **21**, 2393 (1965); Ratuský and Šorm, *Chem. Ind. (London)* **1966**, 1798.

When polyalkyl- or polyhalobenzenes are treated with sulfuric acid, the ring is sulfonated, but, in addition, rearrangement takes place.[231] The reaction, known as the *Jacobsen reaction,* is limited to benzene rings which have at least four substituents, which may be any combination of alkyl and halogen groups, where the alkyl groups may be ethyl or methyl and the halogen iodo, chloro, or bromo. When isopropyl or *tert*-butyl groups are on the ring, these groups are cleaved to give olefins. Since a sulfo group may later be removed (reaction **1-43**), the Jacobsen reaction may be used as a means of rearranging polyalkylbenzenes. Side products in the case illustrated above are pentamethylbenzenesulfonic acid, 2,4,5-trimethylbenzenesulfonic acid, etc., indicating an intermolecular process, at least partially.

At first glance the mechanism seems fairly obvious and in accord with the other reactions in this chapter. That is, SO_3 attacks the ring at a position occupied by an alkyl group, and the alkyl group thus freed migrates inter- or intramolecularly to another position.[232] However, labeling experiments have shown that matters are not so simple. When the reaction was run on polymethylbenzenes labeled in the ring or in the alkyl groups, essentially complete scrambling was found in *both* the ring and the methyl groups.[233] This means that a symmetrical intermediate or a rapidly equilibrating group of intermediates is necessary. Bohlmann and Riemann postulated the following mechanism:



---

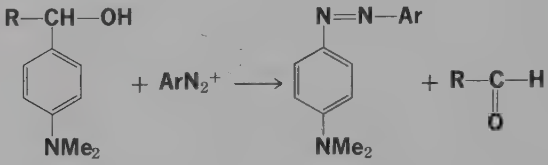
[231] For a review, see Smith, *Org. Reactions* **1,** 370–84 (1942).

[232] For a discussion of the mechanism, see Suzuki, *Bull. Chem. Soc. Japan* **36,** 1642 (1963).

[233] Bohlmann and Riemann, *Chem. Ber.* **97,** 1515 (1964).

In this mechanism, **58**, **59**, and **60** represent a group of rapidly equilibrating intermediates, any of which may react with H_2SO_4 in the manner shown for **59**. These intermediates are free radicals and contain an aromatic system of five electrons. So far there is no corroboration of this idea. It has been shown by labeling that ethyl groups migrate without rearrangement.[234]

1-42 The Stiles-Sisti reaction



α-Hydroxyalkyl groups are replaced by azo groups when there is a dialkylamino group in the para position. The reaction is similar to reaction **1-4**, except that the leaving group is not hydrogen. The reaction is used to prepare aldehydes[235] and ketones.[236]

α-Hydroxyalkyl groups have also been replaced by halogen.[237] In this case too, best results are obtained when there is an activating group in the para position.

OS **44**, 4.

B. Oxygen leaving groups

1-43 Reduction of aromatic ethers

$$\text{ArOR} \xrightarrow{\text{Raney Ni}} \text{ArH} + \text{RH}$$

Aromatic ethers may be reductively cleaved by heating with Raney nickel.[238] The hydrogen comes from that normally contained in this material, and from the solvent. R may also be aromatic, but if it is, it is usually reduced to a cyclohexane ring, unless degassed Raney nickel is used. The mechanism proposed is that, on the surface of the catalyst,

$$\text{Ar—O—R} + \text{H}^- \text{ (from the catalyst)} \longrightarrow \text{Ar}^- + \text{ROH}$$

The Ar^- takes a proton from the solvent. The ROH is then reduced as in reaction **0-74** (p. 349). This mechanism is similar to the carboxylate ion mechanism in reaction **1-40**. With diaryl ethers, cleavage takes place so that the more stable carbanion is formed.

---

[234] Marvell and Webb, *J. Org. Chem.* **27**, 4408 (1962).

[235] Stiles and Sisti, *J. Org. Chem.* **25**, 1691 (1960); Sisti, Burgmaster, and Fudim, *J. Org. Chem.* **27**, 279 (1962).

[236] Sisti, Sawinski, and Stout, *J. Chem. Eng. Data* **9**, 108 (1964).

[237] Clarke and Esselen, *J. Am. Chem. Soc.* **33**, 1135 (1911); Sarkanen and Dence, *J. Org. Chem.* **25**, 715 (1960); Arnett and Klingensmith, *J. Am. Chem. Soc.* **87**, 1023, 1032, 1038 (1965).

[238] Chandler and Sasse, *Australian J. Chem.* **16**, 20 (1963).

C. Sulfur leaving groups

1-44 Desulfonation

$$\mathrm{ArSO_3H} \xrightarrow[\text{dil. } \mathrm{H_2SO_4}]{135\text{–}200^\circ} \mathrm{ArH} + \mathrm{H_2SO_4}$$

The cleavage of sulfo groups from aromatic rings is the reverse of reaction **1-7**.[238a] The reaction permits the sulfo group to be used as a blocking group to direct meta and then to be removed. Migration has also been found, so that *ortho*-methylbenzenesulfonic acid has been converted to *para*-methylbenzenesulfonic acid.[239] The sulfo group has also been replaced by nitro and halogen groups. Sulfo groups have also been removed from the ring by heating with an alkaline solution of Raney nickel.[240]

OS **I**, 388; **II**, 97; **III**, 262; **IV**, 364. Also see OS **I**, 519; **II**, 128; **40**, 99.

D. Halogen leaving groups

1-45 Dehalogenation

$$\mathrm{ArX} \xrightarrow{\mathrm{AlCl_3}} \mathrm{ArH}$$

Aryl halides can be dehalogenated by Friedel-Crafts catalysts, although, except for iodine, the equilibrium lies in the other direction (reaction **1-11**). Not surprisingly, iodine is the most easily cleaved. Dechlorination is seldom performed, and defluorination apparently never. The reaction is most successful when a reducing agent, say $\mathrm{Br^-}$ or $\mathrm{I^-}$, is present to combine with the $\mathrm{I^+}$ or $\mathrm{Br^+}$ coming off.[241] Except for deiodination, the reaction is seldom used for preparative purposes. Migration of halogen is also found, both intramolecular and intermolecular.[242] An example of the latter was conversion of *p*-dibromobenzene to a mixture containing 6% *ortho*-, 59% *meta*-, and 35% *para*-dibromobenzene as well as bromobenzene and some tribromobenzenes, by heating at 200° with $\mathrm{AlBr_3}$.[243] On the other hand, radioactive labeling showed that the $\mathrm{AlCl_3}$-catalyzed isomerization of *ortho*-dichlorobenzene to a mixture consisting mostly of *meta*-dichlorobenzene was largely intramolecular.[244]

The reaction is useful for preparing polyiodo aromatics. Thus 2,4,5,6-tetraiodo-1,3-dimethylbenzene was prepared by treatment of 4,6-diiodo-1,3-

---

[238a] For a review see Gilbert, Ref. 79, pp. 427–442.

[239] Syrkin, Yakerson, and Shnol, *J. Gen. Chem. USSR* **29**, 189 (1960); Wanders and Cerfontain, *Proc. Chem. Soc.* **1963**, 174.

[240] Feigl, *Angew. Chem.* **73**, 113 (1961).

[241] Pettit and Piatak, *J. Org. Chem.* **25**, 721 (1960).

[242] Olah, Tolgyesi, and Dear, *J. Org. Chem.* **27**, 3441, 3449, 3455 (1962); Olah and Meyer, *J. Org. Chem.* **27**, 3464 (1962).

[243] Kooyman and Louw, *Rec. trav. chim.* **81**, 365 (1962); Augustijn, Kooyman, and Louw, *Rec. trav. chim.* **82**, 965 (1963).

[244] Koptyug, Isaev, Gershtein, and Berezovskii, *J. Gen. Chem. USSR* **34**, 3830 (1964).

dimethylbenzene with sulfuric acid.[245] The mechanism is probably the reverse of that of reaction **1-11**.[246,242]

Removal of halogen from aromatic rings can also be accomplished by various reducing agents, among them Ph_3SnH,[247] HI, Sn and HBr, Ph_3P,[248] hydrazine and palladium-charcoal,[249] catalytic hydrogenation, $LiAlH_4$,[250] and Raney nickel in alkaline solution,[251] the latter method being effective for fluorine as well as for the other halogens. Not all of these reagents operate by electrophilic substitution mechanisms. Some are nucleophilic substitutions and some free-radical processes. Rearrangement of polyhalobenzenes may also occur by a nucleophilic mechanism.[252]

OS **III**, 132, 475, 519; **44**, 9, 34.

1-46 Formation of organometallic compounds

$$\mathrm{ArBr} + \mathrm{M} \longrightarrow \mathrm{ArM}$$

$$\mathrm{ArBr} + \mathrm{RM} \longrightarrow \mathrm{ArM} + \mathrm{RBr}$$

These reactions are considered along with their aliphatic counterparts (reactions **2-24** and **2-25**, pp. 475–476).

E. Metal leaving groups

1-47 Hydrolysis of organometallic compounds

$$\mathrm{ArM} + \mathrm{H}^+ \longrightarrow \mathrm{ArH} + \mathrm{M}^+$$

Organometallic compounds can be hydrolyzed by acid treatment. For active metals such as Mg, Li, etc., water is sufficiently acidic. The most important example of this reaction is hydrolysis of Grignard reagents, but M may be many other metals or metalloids. Examples are SiR_3, HgR, Na, $B(OH)_2$. Since aryl Grignard and aryllithium compounds are fairly easy to prepare, they are often used to prepare salts of weak acids, e.g.,

$$\mathrm{PhMgBr} + \mathrm{H{-}C{\equiv}C{-}H} \longrightarrow \mathrm{H{-}C{\equiv}C^-}\quad \mathrm{MgBr^+} + \mathrm{PhH}$$

Where the bond between the metal and the ring is covalent, the usual σ-complex mechanism operates. Where the bonding is essentially ionic, this is a simple acid-base reaction. Other electrophiles can replace metals. For example, azo compounds can be prepared by attack of diazonium ions on arylzinc or -mercury compounds[253] or on Grignard reagents.[254] For the aliphatic counterpart of this reaction, see reaction **2-14** (p. 470).

---

[245] Suzuki and Goto, *Bull. Chem. Soc. Japan* **36**, 389 (1963).

[246] Choguill and Ridd, *J. Chem. Soc.* **1961**, 822.

[247] Rothman and Becker, *J. Org. Chem.* **24**, 294 (1959); Lorenz, Shapiro, Stern, and Becker, *J. Org. Chem.* **28**, 2332 (1963).

[248] Hoffmann, Horner, Wippel, and Michael, *Chem. Ber.* **95**, 523 (1962); Hoffmann and Michael, *Chem. Ber.* **95**, 528 (1962).

[249] Mosby, *Chem. Ind. (London)* **1959**, 1348; *J. Org. Chem.* **24**, 421 (1959).

[250] Karabatsos, Shone, and Scheppele, *Tetrahedron Letters* **1964**, 2113.

[251] Buu-Hoï, Xuong, and van Bac, *Bull. Soc. chim. France* **1963**, 2442.

[252] Moyer and Bunnett, *J. Am. Chem. Soc.* **85**, 1891 (1963).

Other reactions of aryl organometallic compounds are treated with their aliphatic analogs: reactions **2-15** through **2-22.**

---

[253] Curtin and Tveten, *J. Org. Chem.* **26,** 1764 (1961).

[254] Nomura, Anzai, Tarao, and Shiomi, *Bull. Chem. Soc. Japan* **37,** 967 (1964); Nomura, *Bull. Chem. Soc. Japan* **34,** 1648 (1961).

CHAPTER TWELVE

Aliphatic Electrophilic Substitution

In Chapter 11 it was pointed out that the most important leaving groups in electrophilic substitution are those which can best exist with an outer shell which is deficient in a pair of electrons. For aromatic systems the most common leaving group is the proton. The proton is also a leaving group in aliphatic systems, but the reactivity depends on the acidity. Protons in saturated alkanes are very unreactive, but electrophilic substitutions are often easily carried out at more acidic positions, for example, α to a carbonyl group, or at an alkynyl position ($RC{\equiv}CH$). Since metallic ions are easily able to bear positive charges, we might expect that organometallic compounds would be especially susceptible to electrophilic substitution, and this is indeed the case.[1] Another important type of electrophilic substitution, known as *anionic cleavage,* involves the breaking of C—C bonds: in these reactions there are carbon leaving groups (reactions **2-26** to **2-32**). A number of electrophilic substitutions at a nitrogen atom are treated at the end of the chapter.

Since a carbanion is what remains when a positive species is removed from a carbon atom, the subject of carbanion structure and stability (Chapter 5) is inevitably related to the material in this chapter. So is the subject of very weak acids and very strong bases (Chapter 8), since the weakest acids are those in which the hydrogen is bound to carbon.

MECHANISMS

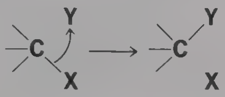
There are three important mechanisms for aliphatic electrophilic substitution reactions, called S_E1, S_E2, and S_Ei.[2]

Bimolecular Mechanisms. S_E2 and S_Ei. The S_E2 mechanism is analogous to the S_N2 (p. 251) in that the new bond is formed as the old one is breaking. However, in the S_N2 mechanism the incoming group brings with it a pair of electrons, and this orbital can overlap with the central carbon only to the extent that the leaving group takes away *its* electrons; otherwise the carbon would have more than eight electrons at once in its outer shell. Since electron clouds repel, this means also that the incoming group attacks backside, at a position 180° from the leaving group, so that inversion of configuration is found. The situation is quite different in the S_E2 mechanism. In this case the incoming group may just as easily approach from the front, since it brings with it only a vacant orbital. Indeed attack at the front is *more* likely, because the electrophile is looking for electrons and that is where the electrons are. So the reaction may be pictured thus:

---

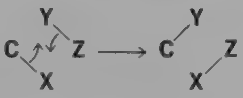
[1] For treatises on the preparation and reactions of organometallic compounds, see Rochow, Hurd, and Lewis, "The Chemistry of Organometallic Compounds," John Wiley & Sons, Inc., New York, 1957; and Coates, "Organometallic Compounds," 2d ed., John Wiley & Sons, Inc., New York, 1960.

[2] This terminology, analogous to that for nucleophilic substitution (Chapter 10), was devised by the Hughes-Ingold school. For reviews of these mechanisms, see Ingold, *Helv. Chim. Acta* **47,** 1191–1203 (1964); *Record Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) **25,** 145–158 (1964) (these two articles are identical, and in English); Köbrich, *Angew. Chem. Intern. Ed. Engl.* **1,** 382–393 (1962); Dessy and Paulik, *J. Chem. Educ.* **40,** 185–194 (1963); Reutov, *Russ. Chem. Rev.* **36,** 163–174 (1967); *Angew. Chem.* **72,** 198–208 (1960); and Cram, *Chem. Eng. News* **41,** No. 33, 92–104 (Aug. 19, 1963).



A reaction following this mechanism should therefore exhibit these characteristics: the kinetics should be first order in each compound, second order overall; and the reaction should proceed with retention of configuration.

The S_Ei mechanism is similar to the S_E2 mechanism with respect to the substrate carbon. The difference is that another part of the attacking entity assists in removal of the leaving group, forming a bond with it at the same time that the new bond is formed between C and Y:



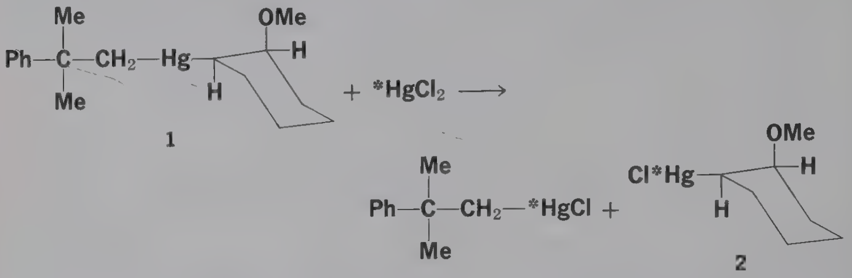
Since this also occurs in only one step and since it is also a frontside attack, this reaction should also exhibit second-order kinetics and retention of configuration. Of course, if inversion should be found in second-order electrophilic substitutions (no examples have ever been reported except in a homoallylic case, see p. 450), it would be compatible with an S_E2 mechanism, since backside attack is not absolutely excluded there, but the S_Ei mechanism could not proceed with backside attack. Some workers prefer to call the S_Ei mechanism the S_F2 mechanism.[3]

Evidence for these mechanisms may be discussed under two aspects: (1) the question as to whether there is a one-step second-order electrophilic substitution that proceeds with retention of configuration, and (2) the question as to whether there are indeed two mechanisms, and, if so, how to tell them apart, since they are alike in the two fundamental respects that both are second order and both involve retention. Indeed, doubts have been expressed as to whether the S_E2 mechanism ever occurs.[3] Taking the first question, it has been demonstrated a number of times that electrophilic substitutions may be second order and proceed with retention. For example, when *cis*-**1** was treated with labeled mercuric chloride, the **2** produced was 100% cis. The bond between the mercury and the ring must have been broken (as well as the other Hg—C bond), since each of the products contained about half of the labeled mercury.[4] Another indication of frontside attack is that second-order electrophilic substitutions proceed very easily at *bridgehead* carbons (see p. 254).[5] Still another indication is the behavior of neopentyl as a substrate. S_N2 reactions at neopentyl are extremely slow (p. 281), because attack from the rear is sterically blocked. The fact that neopentyl systems undergo electrophilic substitution only slightly more slowly than ethyl[6] is further evidence for frontside attack. One final elegant experiment may be noted. The compound di-*sec*-butylmercury was prepared, with one *sec*-butyl group optically active and the other racemic.[7] This was accomplished by treatment of optically active *sec*-butylmercuric bromide with racemic *sec*-butylmagnesium bromide. The di-*sec*-butyl compound was then treated with mercuric bromide to give 2 moles of *sec*-butylmercuric bromide. The steric course of the reaction could then be predicted by the following analysis, assuming that the bonds between the mercury and each carbon have a 50% chance of breaking:

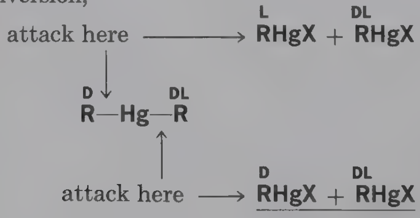
---

[3] See Dessy and Kim, *J. Am. Chem. Soc.* **83**, 1167 (1961); Dessy, Budde, and Woodruff, *J. Am. Chem. Soc.* **84**, 1172 (1962).

[4] Winstein, Traylor, and Garner, *J. Am. Chem. Soc.* **77**, 3741 (1955).

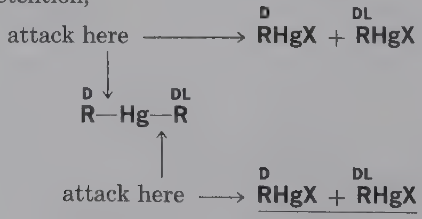


If inversion,



The sum is a racemic mixture

If retention,



The sum has one-half of the original activity

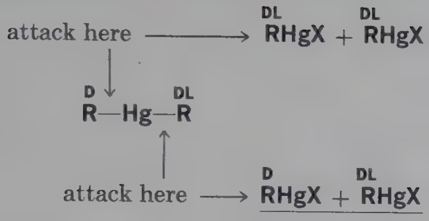
---

[5] Winstein and Traylor, *J. Am. Chem. Soc.* **78,** 2597 (1956); Schöllkopf, *Angew. Chem.* **72,** 147–159 (1960).

[6] Hughes and Volger, *J. Chem. Soc.* **1961,** 2359.

[7] Jensen, *J. Am. Chem. Soc.* **82,** 2469 (1960); Ingold, Ref. 2.

If racemization,



The sum has one-quarter of the original activity

The original activity referred to is the activity of the optically active *sec*-butylmercuric bromide which was used to make the dialkyl compound. The actual result was that, under several different sets of conditions, the product had one-half of the original activity, demonstrating retention of configuration.

At this point might be mentioned the difficulty in preparing compounds which are optically active because of an asymmetric carbon at which a carbon-metal bond is located. This type of optically active compound is difficult to synthesize and is easily racemized. The synthesis has been accomplished most often with organomercury compounds. Only recently has an optically active Grignard reagent been prepared[8] (that is, one in which the only asymmetric center is the carbon bonded to magnesium).

Now that we have established that second-order attack is frontside, we may turn to the question of distinguishing between the S_E2 and S_Ei mechanisms. Despite the essential similarity of the two mechanisms, a way of distinguishing them has been devised, which involves making the Z group more attractive to the X. If this makes the reaction go faster, then it is evidence for the S_Ei mechanism, since bond formation between X and Z occurs in the rate-determining (the only) step and anything which assists this bond formation should increase the rate of an S_Ei reaction. On the other hand, if the rate is not increased, this fact is evidence for the S_E2 mechanism. One such experiment was the reaction, mentioned above, between *sec*-butylmercury and metallic halides.[9] If the mechanism is S_Ei, then $LiHgBr_3$ should react faster than $HgBr_2$, since the former has three bromines with which the leaving mercury can bond, while the latter has only two. On the other hand, if the reaction follows the S_E2 mechanism, then $LiHgBr_3$ should react more slowly, since the charge on the attacking mercury is less in this compound than in $HgBr_2$ (both reactions are second order, and both involve retention). The rate was slower with $LiHgBr_3$, indicating that the mechanism here was S_E2. However, the more positive $Hg(OAc)_2$ and $Hg(NO_3)_2$ reacted faster than $HgBr_2$ (these reactions were also second order and involved retention). The foregoing is evidence for the existence of the S_E2 mechanism. Evidence for the existence of the S_Ei mechanism comes from the exchange reaction between *sec*-butylmercuric bromide and labeled mercuric bromide:

---

[8] Walborsky and Young, *J. Am. Chem. Soc.* **86**, 3288 (1964).

[9] Charman, Hughes, and Ingold, *J. Chem. Soc.* **1959**, 2523, 2530.

$$sec\text{-}Bu{-}HgBr + {}^*HgBr_2 \rightleftharpoons sec\text{-}Bu{-}{}^*HgBr + HgBr_2$$

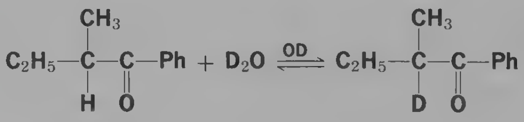
This reaction is also second order and involves retention. It is catalyzed by I^-, Br^-, Cl^-, and acetate ion, in that order.[10] All of these ions are known to coordinate with mercury, and the strength of the coordination is in the same order, so that the actual attacking species in the presence of these ions is, for example, $HgBr_2I^-$. On the other hand, acetic acid and nitrate ion, neither of which coordinate with mercury, do not catalyze the reaction. Since a change in Z increased the rate of the reaction, it is likely that this is a demonstration of the existence of the S_Ei mechanism.

The S_E1 Mechanism. The S_E1 mechanism is analogous to the S_N1 (p. 256). It involves two steps: a slow ionization and a fast combination.

$$1. \quad R{-}X \xrightarrow{\text{Slow}} \bar{R}^- + X^+$$

$$2. \quad \bar{R}^- + Y^+ \longrightarrow R{-}Y.$$

First-order kinetics are predicted, and many such examples have been found. Other evidence for the S_E1 mechanism was obtained in a study of base-catalyzed tautomerism. In the reaction



$$C_2H_5{-}\overset{CH_3}{\underset{H}{C}}{-}\underset{\underset{O}{\|}}{C}{-}Ph + D_2O \xrightleftharpoons{OD} C_2H_5{-}\overset{CH_3}{\underset{D}{C}}{-}\underset{\underset{O}{\|}}{C}{-}Ph$$

Optically active

the rate of deuterium exchange was the same as the rate of racemization,[11] and there *was* an isotope effect.[12] S_N1 reactions do not proceed at bridgehead carbons (p. 258) because, at these carbons, planar carbonium ions cannot form. However, carbanions not stabilized by resonance are probably not planar, and S_E1 reactions should readily occur with this type of substrate. This is the case.[5]

Indeed the question of carbanion structure is intimately tied into the problem of the stereochemistry of the S_E1 reaction. If a carbanion is planar (as are carbonium ions), then racemization should occur. If it is pyramidal and *can hold its structure,* then the result should be retention of configuration. On the other hand, even a pyramidal carbanion will give racemization if it cannot hold its structure, that is, if there is an umbrella effect as with amines (p. 75). Unfortunately the only carbanions that can be easily studied are those stabilized by resonance, which makes them planar, as expected (p. 147). For simple alkyl carbanions, the main approach to determining their structures has been to study the stereochemistry of S_E1 reactions, rather than the other way around. What is found is almost always racemization. Whether this is caused by planar carbanions or by oscillating pyramidal carbanions is not known. In either case racemization occurs whenever a carbanion is completely free or is symmetrically solvated.

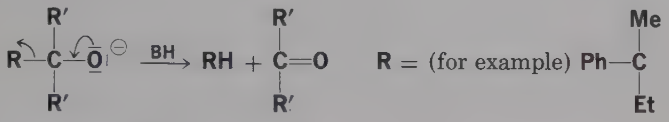
---

[10] Charman, Hughes, Ingold, and Volger, *J. Chem. Soc.* **1961,** 1142.

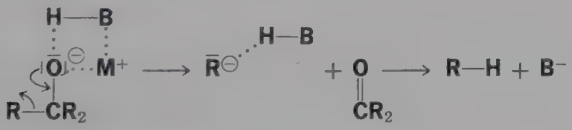
[11] Hsu, Ingold, and Wilson, *J. Chem. Soc.* **1938,** 78.

[12] Wilson, *J. Chem. Soc.* **1936,** 1550.

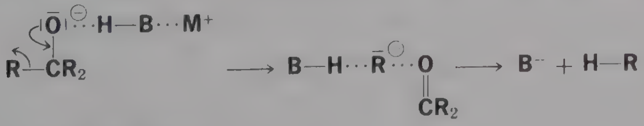
However, even planar carbanions need not give racemization. Cram has found that retention and even inversion may occur in the alkoxide cleavage reaction (**2-27**):



which is a first-order, S_E1 reaction involving resonance-stabilized planar carbanions (here designated as R^-).[13] By changing the solvent Cram was able to produce products ranging from 99% retention to 60% inversion and including complete racemization. These results are explained by a carbanion which is not completely free but is solvated. In nondissociating, nonpolar solvents, such as benzene or dioxane, the alkoxide ion exists as an ion pair, which is solvated by the solvent, BH:



In the course of the cleavage, the proton of the solvent moves in to solvate the newly forming carbanion. As is easily seen, this solvation is asymmetric, since the solvent molecule is already on the front side of the carbanion. When the carbanion actually bonds with the proton, the result is retention of the original configuration. In protic solvents, such as diethylene glycol, a good deal of inversion is found. In these solvents, the *leaving group* solvates the carbanion, so that the solvent can solvate it only from the opposite side:

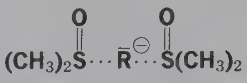


Solvent-separated
ion pair

When C—H bond formation occurs, the result is inversion. Racemization results in polar aprotic solvents like dimethyl sulfoxide. In these solvents the carbanions are relatively long-lived (because the solvent has no proton to donate) and symmetrically solvated:

---

[13] Cram, Langemann, Allinger, and Kopecky, *J. Am. Chem. Soc.* **81**, 5740 (1959); Cram, Langemann, and Hauck, *J. Am. Chem. Soc.* **81**, 5750 (1959); Cram, Kopecky, Hauck, and Langemann, *J. Am. Chem. Soc.* **81**, 5754 (1959); Cram, Mateos, Hauck, Langemann, Kopecky, Nielsen, and Allinger, *J. Am. Chem. Soc.* **81**, 5774 (1959). For a discussion, see Cram, "Fundamentals of Carbanion Chemistry," pp. 138–158, Academic Press Inc., New York, 1965.



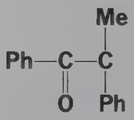
$$(CH_3)_2\overset{\overset{O}{\|}}{S}\cdots\bar{R}^{\ominus}\cdots\overset{\overset{O}{\|}}{S}(CH_3)_2$$

Similar behavior was found for carbanions generated by base-catalyzed hydrogen exchange (reaction **2-1**):[14]

$$R{-}H + B{-}D \xrightleftharpoons{B^-} R{-}D + B{-}H$$

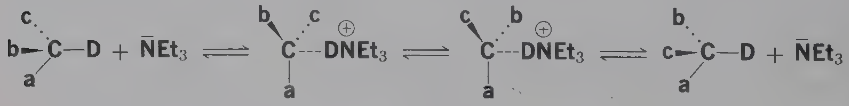
B^- = base

R = (for example)



$$Ph{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{Me}{|}}{\underset{\underset{Ph}{|}}{C}}$$

In this case information was obtained from measurement of the ratio of k_e (rate constant for isotopic exchange) to k_α (rate constant for racemization). A k_e/k_α ratio substantially greater than 1 means retention of configuration, since many individual isotopic exchanges are not producing a change in configuration. A k_e/k_α ratio of about 1 indicates racemization, and a ratio of $\frac{1}{2}$ corresponds to inversion (see p. 255). All three types of steric behavior were found, depending on R, the base, and the solvent. As with the alkoxide cleavage reaction, retention was generally found in solvents of low dielectric constant, racemization in polar aprotic solvents, and inversion in protic solvents. However, in the proton exchange reactions, a fourth type of behavior was encountered. In aprotic solvents, with aprotic bases like tertiary amines, the k_e/k_α ratio was found to be *less* than 0.5, indicating that racemization was taking place *faster* than isotopic exchange. Under these conditions, the conjugate acid of the amine remains associated with the carbanion as an ion pair. Occasionally, the ion pair dissociates long enough for the carbanion to turn over and recapture the proton:

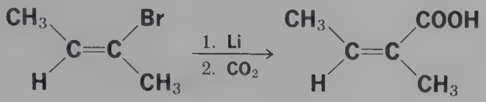


Thus, inversion (and hence racemization, which is produced by repeated acts of inversion) occurs without exchange. This process is known as *isoracemization*. Of course, the four types of steric behavior are not mutually exclusive, and two or more processes often operate simultaneously.

It is known that olefinic carbanions *can* maintain configuration, so that S_E1 mechanisms should produce retention there. This has been found to be the case. For example, *trans*-2-bromo-2-butene was converted to 64–74% angelic acid:[15]

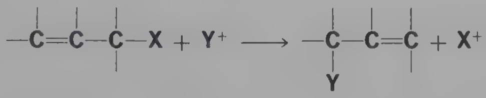
---

[14] Cram, Kingsbury, and Rickborn, *J. Am. Chem. Soc.* **83,** 3688 (1961); Cram, Rickborn, Kingsbury, and Haberfield, *J. Am. Chem. Soc.* **83,** 3678 (1961); Cram and Gosser, *J. Am. Chem. Soc.* **85,** 3890 (1963); **86,** 5445, 5457 (1964); Cram and Wingrove, *J. Am. Chem. Soc.* **86,** 5490 (1964). For a discussion, see Cram, Ref. 13, pp. 85–105.



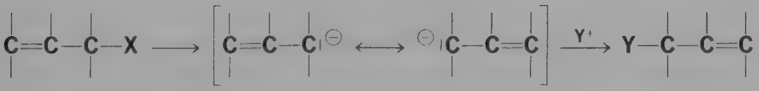
Only about 5% of the cis isomer, tiglic acid, was produced. In addition, certain carbanions in which the negative charge is stabilized by *d*-orbital overlap can maintain configuration (p. 148), and S_E1 reactions involving them proceed with retention of configuration.

Electrophilic Substitution Accompanied by Double-bond Shifts. When electrophilic substitution is carried out at an allylic substrate, the product may be rearranged:

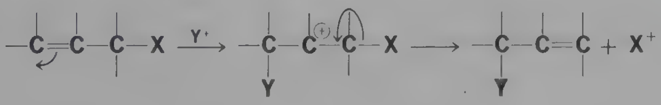


$$-C{=}C-C-X + Y^+ \longrightarrow -\underset{Y}{C}-C{=}C + X^+$$

This type of process is analogous to the nucleophilic allylic shifts discussed in Chapter 10 (p. 270). There are two principal pathways. The first of these is analogous to the S_E1 mechanism, in that the leaving group is first removed, giving a resonance-stabilized allyl type of carbanion, and then the electrophile attacks.



In the other pathway the Y group first attacks, giving a carbonium ion, which then loses X.

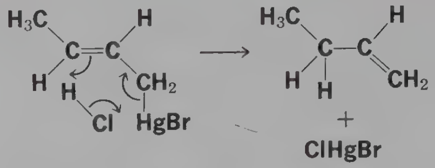


These mechanisms are more fully discussed under reaction **2-2.**

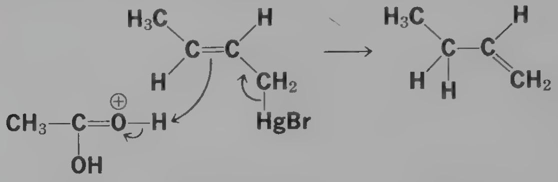
Most electrophilic allylic rearrangements involve hydrogen as the leaving group, but they have also been observed with metallic leaving groups. Sleezer, Winstein, and Young found that crotylmercuric bromide reacted with HCl about 10^7 times faster than *n*-butylmercuric bromide, and the product was more than 99% 1-butene.[16] These facts point to an S_Ei' mechanism:

---

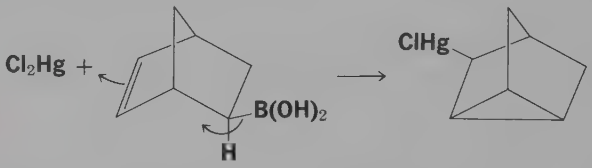
[15] Dreiding and Pratt, *J. Am. Chem. Soc.* **76**, 1902 (1954).



The reaction of the same compound with acetic acid–perchloric acid seems to proceed by an S_E2' mechanism:[16]



In one electrophilic rearrangement (actually a *homoallylic* rearrangement), inversion was found, this being the only case so far of inversion accompanying second-order electrophilic substitution.[17] In this reaction, the exo isomer of **3** reacted hundreds of times faster than the endo isomer, which also gave the reaction, but with retention of configuration:



3

Other Mechanisms. Elimination-addition (see reaction **2-1**), addition-elimination (reaction **2-9**), and cyclic mechanisms (reaction **2-26**) are also known.

Much less work has been done on electrophilic aliphatic substitution mechanisms than on nucleophilic substitutions, and the exact mechanisms of many of the reactions in this chapter are in doubt. For many of them, not enough work has been done to permit us to decide which of the mechanisms described in this chapter is operating, if indeed any is. There may be other electrophilic substitution mechanisms, and some of the reactions in this chapter may not even be electrophilic substitutions at all.

REACTIVITY

Only a small amount of work has been done in this area, in comparison to the vast amount done for aliphatic nucleophilic substitution and aromatic electrophilic substitution. Only a few conclusions, most of them sketchy or tentative, can be drawn.

---

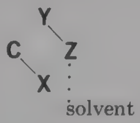
[16] Sleezer, Winstein, and Young, *J. Am. Chem. Soc.* **85,** 1890 (1963).

[17] Matteson and Waldbillig, *J. Am. Chem. Soc.* **86,** 3778 (1964).

1. *Effect of substrate.* For S_E1 reactions electron-donating groups decrease rates and electron-withdrawing groups increase them.[18] This is as would be expected from a reaction in which the rate-determining step is analogous to the cleavage of a proton from an acid. For second-order reactions the facts are contradictory. Rate orders of Me > Et > *iso*-Pr > *tert*-Bu,[19] of vinyl > phenyl > Et > *iso*-Pr > Pr > Me,[20] and of *tert*-Bu > *sec*-Bu > Bu > vinyl > phenyl > Me[21] have been reported. Obviously this type of mechanism is sensitive to relatively small changes in conditions.

2. *Effect of leaving group.* The more polar the C—X bond, the more likely would seem the S_E1 mechanism, since the lower the electron density on X, the easier it is for X to leave. It has been shown that changing the leaving group from HgBr to the more electronegative HgCl decreases the rate,[22] as would be expected from this prediction. It might be further expected that, when metals are the leaving groups, S_E1 mechanisms would be favored, while with carbon leaving groups, second-order mechanisms would be found. However, the results so far reported have been just about the reverse of this. For carbon leaving groups the mechanism is usually S_E1, while for metallic leaving groups, until recently, only S_E2 or S_Ei processes were found. That S_E1 mechanisms *could* take place with a metallic leaving group was shown by Reutov,[18] Hughes and Ingold[22] and their coworkers, who studied the exchange reaction between α-carbethoxybenzylmercuric halides and radioactive mercuric halides.[22a] The kinetics were first order, and the product was racemized.

3. *Effect of solvent.* In addition to the solvent effects on certain S_E1 reactions, mentioned earlier (p. 447), solvents can influence the mechanism which is preferred. As with nucleophilic substitution (p. 293), an increase in solvent polarity increases the possibility of an ionizing mechanism, in this case S_E1, in comparison with the second-order mechanisms, which do not involve ions. The solvent should also exert an influence as between the S_E2 and S_Ei mechanisms. In polar solvents S_E2 mechanisms should be favored at the expense of S_Ei, since in these solvents Z would be solvated, leaving it less free to attack X:[23]



---

[18] Reutov, Sokolov, and Beletskaya, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1961,** 1328; Reutov, Praisnar, Beletskaya, and Sokolov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963,** 884.

[19] Kreevoy and Hansen, *J. Am. Chem. Soc.* **83,** 626 (1961).

[20] Dessy, Reynolds, and Kim, *J. Am. Chem. Soc.* **81,** 2683 (1959).

[21] Minato, Ware, and Traylor, *J. Am. Chem. Soc.* **85,** 3024 (1963).

[22] Hughes, Ingold, and Roberts, *J. Chem. Soc.* **1964,** 3900.

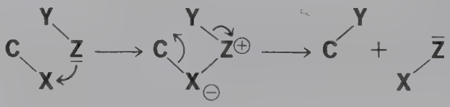
[22a] Another example of an S_E1 mechanism with a metallic leaving group was reported by Hart and Ingold, *J. Chem. Soc.* **1964,** 4372, but this has been challenged by Jensen and Heyman, *J. Am. Chem. Soc.* **88,** 3438 (1966).

[23] Gielen and Nasielski, *Rec. trav. chim.* **82,** 228 (1963).

Results have been found in accord with this prediction, but since the conclusions are based on reactivity order in second-order reactions, we have seen (p. 451) that they must be taken with great caution. These results are as follows: it has been found that in polar solvents, such as methanol, acetic acid, or dimethylformamide, where S_E2 mechanisms would be favored (as against S_Ei), the second-order rate constants for the reaction

$$R_4Sn + X_2 \longrightarrow R_3SnX + RX$$

were in the order Me > Et > Pr > *iso*-Pr.[24] This is interpreted as a purely steric sequence. In less polar solvents, such as chlorobenzene or carbon tetrachloride, the order was Me < Et > Pr < *iso*-Pr. This order is ascribed to a combination of steric and inductive effects. Some reactions have been found which do not follow either sequence, but rather a strict polarity sequence: Me < Et, Pr < *iso*-Pr < *tert*-Bu.[25] It has been suggested that in such cases the mechanism involves initial bond formation between the leaving group (before it becomes detached) and the electrophile, and a subsequent bond-breaking step



This process has been called the S_EC mechanism.[25]

REACTIONS

The reactions in this chapter are arranged in order of leaving group: hydrogen, metals, halogen, and carbon. Lastly are treated electrophilic substitutions at a nitrogen atom. The following reactions, treated in other chapters, are also electrophilic substitutions, with respect to the attacking molecule: **0-81** to **0-98**, **0-104**, **3-11** to **3-15**, **5-14**, **5-15**, **5-20**, **5-39**, and **6-31** to **6-53**.

Hydrogen as Leaving Group

A. Hydrogen as the electrophile

2-1 Hydrogen exchange

$$R{-}H + D^+ \rightleftharpoons R{-}D + H^+$$

As with reaction **1-1** (p. 396), the hydrogen exchange reaction is mostly used to study mechanistic questions. Only fairly acidic protons, e.g., acetylenic, allylic, etc., exchange with acids. Primary, secondary, and tertiary alkyl hydrogens generally do not, although there are some special cases. The methyl protons of $ArC(CH_3)_3$ exchange with D^+, but this mechanism is complicated and involves the ring.[26] The mechanism of the normal reaction is probably S_E2 or S_Ei. Exchange may also be carried out with bases, in which case the mechanism is undoubtedly S_E1 (see p. 448):

---

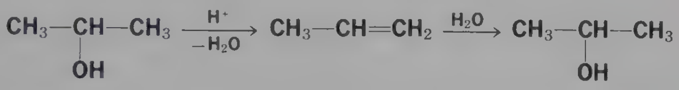
[24] Gielen and Nasielski, *J. Organometal. Chem.* **1**, 173 (1963).

[25] Abraham and Hill, *J. Organometal. Chem.* **7**, 11 (1967).

$$1. \quad RH + B^- \longrightarrow R^- + BH$$

$$2. \quad R^- + BD \longrightarrow RD + B^-$$

Even weakly acidic protons exchange with bases (see p. 143). Still another mechanism has been found for the slow acid exchange of hydrogens β to an OH group (such as the methyl protons in 2-propanol). This is an elimination-addition mechanism, in which the alcohol is first dehydrated (reaction **7-1,** p. 753) and then water re-adds (reaction **5-2,** p. 581):[27]



$$CH_3{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_3 \xrightarrow[-H_2O]{H^+} CH_3{-}CH{=}CH_2 \xrightarrow{H_2O} CH_3{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_3$$

2-2 Migration of double bonds[28]

$$CH_3{-}CH_2{-}CH{=}CH_2 \xrightarrow{H^+} CH_3{-}CH{=}CH{-}CH_3$$

The double bonds of many unsaturated compounds are shifted on treatment with acids. Both proton acids and Lewis acids may be used. In many instances equilibrium mixtures of two or more compounds are obtained, but the most thermodynamically stable olefin predominates. This is an example of an electrophilic substitution with accompanying allylic shift. With proton acids the reaction occurs in two steps:

$$1. \quad CH_3{-}CH_2{-}CH{=}CH_2 + H^+ \longrightarrow CH_3{-}CH_2{-}\overset{\oplus}{CH}{-}CH_3$$

$$2. \quad CH_3{-}CH_2{-}\overset{\oplus}{CH}{-}CH_3 \longrightarrow CH_3{-}CH{=}CH{-}CH_3 + H^+$$

The proton attacks at that side of the double bond which gives the more stable carbonium ion (see Markovnikov's rule, p. 576). Which proton leaves depends on the structure of the carbonium ion. If the new double bond can be in conjugation with one already present, or with an aromatic ring, it goes that way. If the choice is between an exocyclic and an endocyclic double bond (in a six-membered ring), it chooses the latter. In the absence of considerations like these, Zaitsev's rule (p. 739) applies, and the proton is lost from that carbon which has the fewest hydrogens. In general the direction of double-bond formation is the same as that for E1 elimination reactions (p. 738). All of these considerations would lead us to predict that terminal olefins can be isomerized to internal ones, nonconjugated olefins to conjugated, exo six-membered-ring olefins to endo, etc., and not the other way around. This is indeed usually the case. Exceptions are known, which do not however violate the rule that the most stable olefin is formed. For example, large cyclic dienes (but with rings smaller than 18-membered) exhibit Pitzer strain when the double bonds are conjugated, but not when they are in certain other locations. In these cases, equilibration results in preferential formation of the more stable nonconjugated isomers.[29]

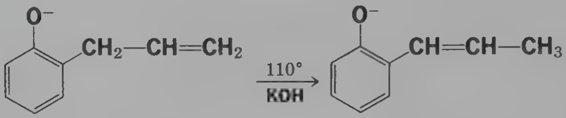
---

[26] Dallinga and ter Maten, *Rec. trav. chim.* **79,** 737 (1960).

[27] Gold and Satchell, *J. Chem. Soc.* **1963,** 1930, 1937.

[28] For a review, see Mackenzie, in Patai, "The Chemistry of Alkenes," pp. 416–436, Interscience Publishers, Inc., New York, 1964.

Double-bond shifts may also be accomplished with basic reagents, for example:[30]



This mechanism is the reverse of the previous one; first a proton is lost, giving a resonance-stabilized carbanion, which then combines with a proton at the position which will give the more stable olefin:

$$1.\quad R{-}CH_2{-}CH{=}CH_2 + B \longrightarrow \left[R{-}\overset{\ominus}{\bar{C}}H{-}CH{=}CH_2 \longleftrightarrow R{-}CH{=}CH{-}\overset{\ominus}{\bar{C}}H_2\right] + BH^+$$

$$2.\quad \left[R{-}\overset{\ominus}{\bar{C}}H{-}CH{=}CH_2 \longleftrightarrow R{-}CH{=}CH{-}\overset{\ominus}{\bar{C}}H_2\right] \xrightarrow{BH^+} R{-}CH_2{=}CH{-}CH_3 + B$$

This mechanism is exactly analogous to the allylic-shift mechanism for nucleophilic substitution, discussed in Chapter 10 (p. 270). Ultraviolet spectra of allylbenzene and 1-propenylbenzene, in solutions containing NH_2^-, are identical, showing that the same carbanion is present in both cases, as required by this mechanism.[31] It has been shown that base-catalyzed double-bond shifts are partially intramolecular, at least in some cases.[32] The intramolecularity probably arises from a process in which the departing proton remains for a time simultaneously hydrogen-bonded to both sites:

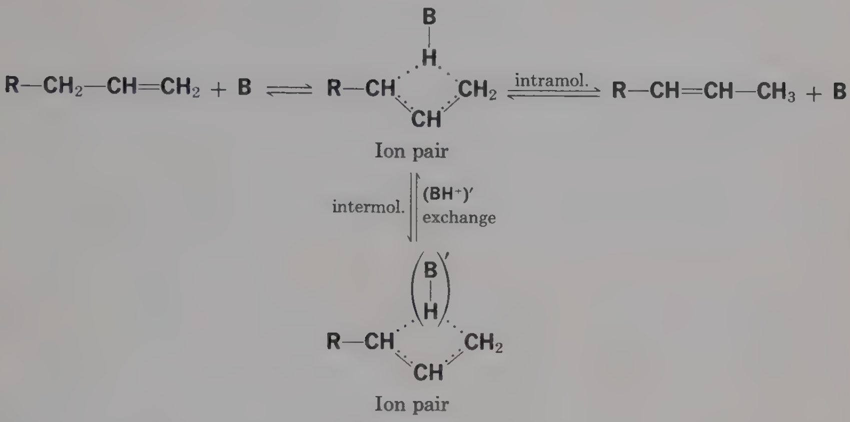
---

[29] Hubert and Dale, *J. Chem. Soc.* **1963**, 4091.

[30] Sherrill and Matlack, *J. Am. Chem. Soc.* **59**, 2134 (1937). For a discussion, see Cram, "Fundamentals of Carbanion Chemistry," pp. 175–210, Academic Press Inc., New York, 1965.

[31] Rabinovich, Astaf'ev, and Shatenshtein, *J. Gen. Chem. USSR* **32**, 746 (1962).

[32] See, for example, Cram and Uyeda, *J. Am. Chem. Soc.* **86**, 5466 (1964); Bank, Rowe, and Schriesheim, *J. Am. Chem. Soc.* **85**, 2115 (1963); Doering and Gaspar, *J. Am. Chem. Soc.* **85**, 3043 (1963); Bergson, *Acta Chem. Scand.* **17**, 2691 (1963).



The ion pair may then collapse to the rearranged olefin (intramolecular process), or another molecule of BH^+ may exchange to give another ion pair, collapse of which gives intermolecular rearrangement.

Triple bonds may also migrate in the presence of bases, but through the allene intermediate:[33]

$$R{-}CH_2{-}C{\equiv}CH \rightleftharpoons R{-}CH{=}C{=}CH_2 \rightleftharpoons R{-}C{\equiv}C{-}CH_3$$

Double-bond isomerization may also take place in other ways. Nucleophilic allylic rearrangements were discussed in Chapter 10 (p. 270). Isomerization of double bonds with HBr or I_2 and ultraviolet light is a free-radical process:[34]

$$HBr \xrightarrow{h\nu} Br\cdot + H\cdot$$

$$CH_3CH_2CH{=}CH_2 + Br\cdot \longrightarrow$$
$$\left[CH_3{-}\dot{C}H{-}CH{=}CH_2 \longleftrightarrow CH_3{-}CH{=}CH{-}\dot{C}H_2\right] + HBr$$

$$CH_3CH{=}CH\dot{C}H_2 + HBr \longrightarrow CH_3CH{=}CHCH_3 + Br\cdot$$

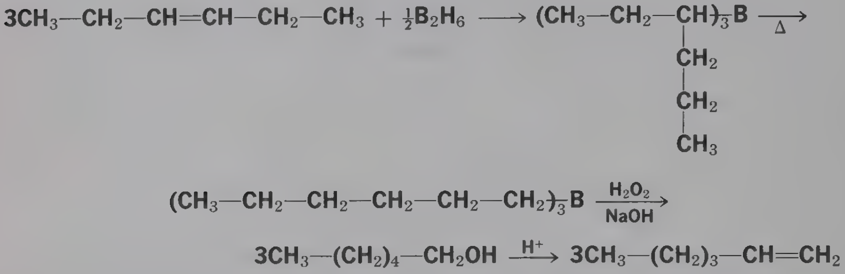
Olefins may also be isomerized upon pyrolysis at, say, 400 to 500°. Carbonium ions are presumably involved.

No matter which of the electrophilic methods of double-bond shifting is employed, the thermodynamically most stable olefin is formed in largest amount in most cases, though a few anomalies are known. However, there is another, indirect, method of double-bond isomerization, by means of which migration in the other direction can often be carried out. This involves conversion of the olefin to a borane (reaction **5-13,** p. 599), rearrangement of the borane (reaction **8-12,** p. 814), oxidation and hydrolysis of the newly formed borane to the alcohol (reaction **9-33,** p. 889), and dehydration of the alcohol (reaction **7-1,** p. 753):

---

[33] For example, see Jacobs and Dankner, *J. Org. Chem.* **22,** 1424 (1957); Bainvel, Wojtkowiak, and Romanet, *Bull. Soc. chim. France* **1963,** 978; Wotiz, Billups, and Christian, *J. Org. Chem.* **31,** 2069 (1966).

[34] Golden, Egger, and Benson, *J. Am. Chem. Soc.* **86,** 5416 (1964); Egger, Golden, and Benson, *J. Am. Chem. Soc.* **86,** 5420 (1964); Maccoll and Ross, *J. Am. Chem. Soc.* **87,** 1169 (1965); Abell, *Trans. Faraday Soc.* **60,** 2214 (1964); *J. Am. Chem. Soc.* **88,** 1346 (1966).



$$3CH_3{-}CH_2{-}CH{=}CH{-}CH_2{-}CH_3 + \tfrac{1}{2}B_2H_6 \longrightarrow (CH_3{-}CH_2{-}\underset{\underset{\underset{CH_3}{|}}{\overset{|}{CH_2}}}{\overset{|}{\underset{CH_2}{CH}}}\!\!)_3B \xrightarrow[\Delta]{}$$

$$(CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2)_3B \xrightarrow[NaOH]{H_2O_2}$$

$$3CH_3{-}(CH_2)_4{-}CH_2OH \xrightarrow{H^+} 3CH_3{-}(CH_2)_3{-}CH{=}CH_2$$

Since the migration reaction is always toward the end of a chain, terminal olefins may be produced from internal ones, so that the migration is often opposite to that with the other methods. Alternatively, the rearranged borane may be converted directly to the olefin by heating with an alkene of higher molecular weight than the product (reaction **7-16,** p. 766).

The reactions involving proton acids, Lewis acids, or pyrolysis are often unsatisfactory for synthetic purposes, since they give rise to many side products characteristic of carbonium-ion mechanisms. If the substrate has several possible locations for a double bond, mixtures of all possible isomers are usually obtained. Isomerization of 1-decene, for example, gives a mixture which not only contains 1-decene and *cis*- and *trans*-2-decene, but also the cis and trans isomers of 3-, 4-, and 5-decene, as well as branched alkenes resulting from rearrangement of carbonium ions. It is true that the most stable olefins predominate, but many of them have stabilities which are close together.

If a hydroxy group is present in the chain, *it* may lose a proton, so that a ketone is the product. For example,[35]

$$R_2C{=}CH{-}CH_2{-}CH_2{-}CHOH{-}CH_3 \xrightarrow[\text{acid}]{\text{polyphosphoric}} R_2CH{-}CH_2{-}CH_2{-}CH_2{-}CO{-}CH_3$$

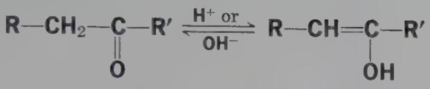
Similarly, α-hydroxy triple-bond compounds have given α,β-unsaturated ketones.

OS **II,** 140; **III,** 207; **IV,** 189, 192, 195, 234, 398, 683.

---

[35] Colonge and Brunie, *Bull. Soc. chim. France* **1963,** 1799.

2-3 Keto-enol tautomerization

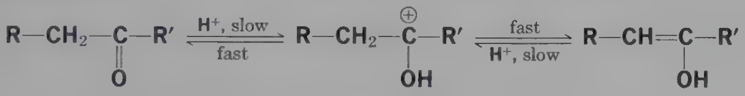


$$R{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}R' \underset{OH^-}{\overset{H^+ \text{ or}}{\rightleftharpoons}} R{-}CH{=}\underset{\underset{OH}{|}}{C}{-}R'$$

The tautomeric equilibrium between enols and ketones or aldehydes is not normally a preparative reaction, although, for some ketones, both forms can be prepared (see p. 59 for a discussion of this and other aspects of tautomerism). For most ketones and aldehydes, only the keto form is detectable, although the equilibrium must be occurring, since aldehydes and ketones often react through their enol forms.

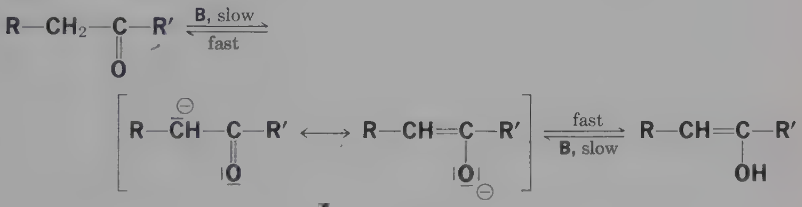
Neither the forward nor the reverse reaction can take place without at least a trace of acid or base, ruling out a direct shift of a hydrogen from carbon to oxygen or vice versa. The mechanisms are identical to those in reaction **2-2**:[36]

Acid-catalyzed



$$R{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}R' \underset{\text{fast}}{\overset{H^+\text{, slow}}{\rightleftharpoons}} R{-}CH_2{-}\underset{\underset{OH}{|}}{\overset{\oplus}{C}}{-}R' \underset{H^+\text{, slow}}{\overset{\text{fast}}{\rightleftharpoons}} R{-}CH{=}\underset{\underset{OH}{|}}{C}{-}R'$$

Base-catalyzed



$$R{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}R' \underset{\text{fast}}{\overset{B\text{, slow}}{\rightleftharpoons}} \left[R{-}\overset{\ominus}{\bar{C}H}{-}\underset{\underset{|\underline{O}}{\|}}{C}{-}R' \longleftrightarrow R{-}CH{=}\underset{\underset{|\underline{O}|^{\ominus}}{|}}{C}{-}R' \right] \underset{B\text{, slow}}{\overset{\text{fast}}{\rightleftharpoons}} R{-}CH{=}\underset{\underset{OH}{|}}{C}{-}R'$$

4

For each catalyst, the mechanism for one direction is the exact reverse of the other, by the law of microscopic reversibility. The base-catalyzed reaction shows an isotope effect (i.e., with RCD_2COR as substrate) of about 5,[37] consistent with a mechanism in which a proton is lost in the rate-determining step. No isotope effect is expected for the acid-catalyzed reaction, but in some cases there is one,[38] showing that in these cases, the second step is slower than the first.

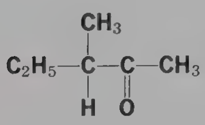
Although the conversion of an aldehyde or a ketone to its enol tautomer is not generally a preparative procedure, the reactions do have their preparative aspects. If a full mole of base per mole of ketone is used, then the enolate ion (**4**) is formed and can be isolated. When enol ethers or esters are hydrolyzed, the enols initially formed immediately tautomerize to the aldehydes or ketones. In addition, the overall processes (forward plus reverse reactions) are often used for equilibration purposes. When an optically active compound in which the dissymmetry is due to an asymmetric carbon α to a carbonyl group (as in **5**) is treated with acid or base, racemization results. If there is another asymmetric center in the molecule, the less stable epimer may be converted to the more stable one in this manner, and this is often done. For example, *cis*-decalone (**6**) may be equilibrated to the trans isomer. Isotopic exchange may also be accomplished at the α position of an aldehyde or ketone, in a similar manner. For the acid-catalyzed process, exchange or equilibration is accomplished only if the carbonyl compound is completely converted to the enol and then back, but in the base-catalyzed process exchange or equilibration can take place if only the first step (conversion to the enolate ion) takes place. The difference is usually academic.

---

[36] For discussions of the mechanism, see Ingold, "Structure and Mechanism in Organic Chemistry," pp. 530–575, Cornell University Press, Ithaca, N.Y., 1953; Bell, "The Proton in Chemistry," pp. 140–143, Cornell University Press, Ithaca, N.Y., 1959.

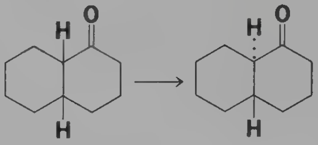
[37] Riley and Long, *J. Am. Chem. Soc.* **84,** 522 (1962).

[38] Kosicki, *Can. J. Chem.* **40,** 1280 (1962).



$$C_2H_5-\underset{H}{\overset{CH_3}{C}}-\underset{\overset{\|}{O}}{C}-CH_3$$

5



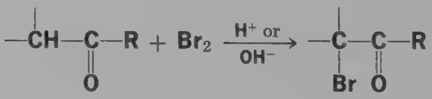
6

Enolizable hydrogens may be replaced by deuterium (and ^{16}O by ^{18}O) by passage of a sample through a deuterated (or ^{18}O-containing) gas-chromatography column.[39]

There are many enol-keto interconversions and acidifications of enolate ions to the keto forms listed in *Organic Syntheses*. No attempt is made to list them here.

B. Halogen electrophiles

2-4 Halogenation of aldehydes and ketones



$$-\overset{|}{CH}-\underset{\overset{\|}{O}}{C}-R + Br_2 \xrightarrow[OH^-]{H^+ \text{ or}} -\underset{Br}{\overset{|}{C}}-\underset{\overset{\|}{O}}{C}-R$$

Aldehydes and ketones may be halogenated in the α position with bromine, chlorine, or iodine.[40] The reaction cannot be performed with fluorine, but active compounds, such as β-keto esters, have been fluorinated by treating the enolate ion with $FClO_3$.[41] However, if the carbon attacked with $FClO_3$ has two hydrogens, then the reaction cannot be stopped until two fluorines have entered. Sulfuryl chloride[42] and cupric chloride[43] have been used as reagents for chlorination, and N-bromosuccinimide for bromination (see reaction **4-2,** p. 535).

---

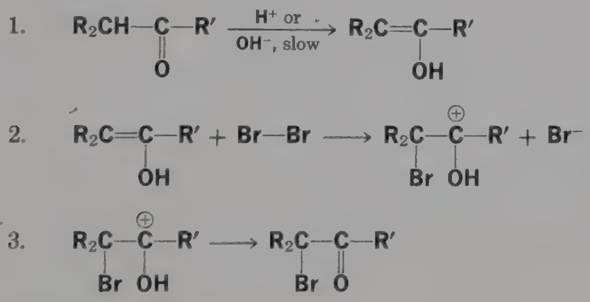
[39] Senn, Richter, and Burlingame, *J. Am. Chem. Soc.* **87**, 680 (1965); Richter, Senn, and Burlingame, *Tetrahedron Letters* **1965**, 1235.

[40] For a review, see House, "Modern Synthetic Reactions," pp. 144–154, W. A. Benjamin, Inc., New York, 1965.

[41] Inman, Oesterling, and Tyczkowski, *J. Am. Chem. Soc.* **80**, 6533 (1958); Machleidt, *Ann.* **667**, 24 (1963); Machleidt and Hartmann, *Ann.* **679**, 9 (1964).

For unsymmetrical ketones the preferred position of halogenation is usually a CH group, then a CH_2 group, and then CH_3; however, mixtures are frequent. With aldehydes the aldehydic hydrogen is sometimes replaced (see reaction **4-3,** p. 538). It is possible to prepare di- and polyhalides too. With acid catalysts the second halogen usually enters on the other side of the carbonyl group (in ketones), even when the ketone is unsymmetrical.[44] When basic catalysts are used, one position is completely halogenated before the other is attacked, and the reaction cannot be stopped until all the hydrogens of the first carbon have been replaced. If one of the groups is methyl, then the haloform reaction (**2-30**) takes place. Sometimes acetals and ketals are brominated directly.

It is not the aldehyde or ketone itself which is halogenated, but the enol form. The purpose of the catalyst is to provide a small amount of enol. The reaction is often done without addition of acid or base, and even in the vapor state,[45] but traces of acid or base are always present, and these are enough to catalyze formation of the enol. The mechanism is



$$1.\quad R_2CH—\underset{\underset{O}{\|}}{C}—R' \xrightarrow[\text{OH}^-\text{, slow}]{\text{H}^+\text{ or}} R_2C{=}\underset{\underset{OH}{|}}{C}—R'$$

$$2.\quad R_2C{=}\underset{\underset{OH}{|}}{C}—R' + Br—Br \longrightarrow R_2\underset{\underset{Br}{|}}{C}—\overset{\oplus}{\underset{\underset{OH}{|}}{C}}—R' + Br^-$$

$$3.\quad R_2\underset{\underset{Br}{|}}{C}—\overset{\oplus}{\underset{\underset{OH}{|}}{C}}—R' \longrightarrow R_2\underset{\underset{Br}{|}}{C}—\underset{\underset{O}{\|}}{C}—R'$$

The first step, as we have already seen (reaction **2-3**), actually consists of two steps. The second step is very similar to the first step in electrophilic addition to double bonds (p. 562). There is a great deal of evidence for this mechanism: (1) the rate is first order in substrate; (2) the bromine does not appear in the rate expression at all, a fact consistent with a rate-determining first step; (3) the rate of the reaction is the same for bromination, chlorination, and iodination, under the same conditions;[46] and (4) the reaction shows an isotope effect.

OS **I,** 127; **II,** 87, 88, 244, 480; **III,** 188, 343, 538; **IV,** 110, 162, 590.

---

[42] Wyman and Kaufman, *J. Org. Chem.* **29,** 1956 (1964).

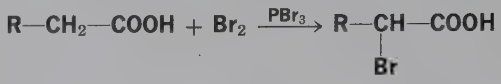
[43] Kosower, Cole, Wu, Cardy, and Meisters, *J. Org. Chem.* **28,** 630 (1963); Kosower and Wu, *J. Org. Chem.* **28,** 633 (1963).

[44] Rappe and Schotte, *Acta Chem. Scand.* **16,** 2060 (1962); Rappe, *Acta Chem. Scand.* **16,** 2467 (1962); *Arkiv Kemi* **21,** 503 (1964); Garbisch, *J. Org. Chem.* **30,** 2109 (1965).

[45] Dick, *J. Org. Chem.* **27,** 272 (1962).

[46] Bell and Yates, *J. Chem. Soc.* **1962,** 1927.

2-5 Halogenation of acids and acyl halides



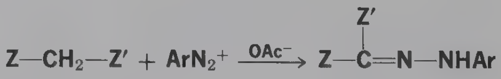
$$R{-}CH_2{-}COOH + Br_2 \xrightarrow{PBr_3} R{-}\underset{\displaystyle Br}{\underset{|}{C}H}{-}COOH$$

The α hydrogens of carboxylic acids may be replaced by bromine or chlorine.[47] The reaction, known as the *Hell-Volhard-Zelinskii reaction,* is not applicable to iodine or fluorine. When there are two α hydrogens, one or both may be replaced, although it is often hard to stop with just one. The reaction actually takes place on the acyl halide formed from the acid and the catalyst. Acids alone are inactive, except for those with relatively high enol content, such as malonic. Less than one full mole of catalyst (per mole of substrate) is required, because of the exchange reaction between acids and acyl halides (see reaction **0-70,** p. 346). Each molecule of acid is α-halogenated while it is in the acyl halide stage. The halogen from the catalyst does not enter the α position. For example, the use of Cl_2 and PBr_3 results in α chlorination, not bromination. As expected from the foregoing, acyl halides undergo α halogenation without a catalyst. So do anhydrides and many compounds which enolize easily, e.g., malonic ester, aliphatic nitro compounds, etc. The mechanism is usually regarded as proceeding through the enol as in reaction **2-4.**[48]

OS **I,** 115, 245; **II,** 74, 93; **III,** 347, 381, 495, 523, 623, 705, 848; **IV,** 254, 348, 398, 608, 616; **45,** 22. Also see OS **IV,** 877.

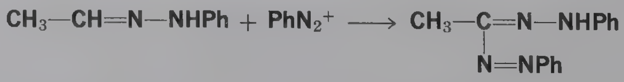
C. Nitrogen electrophiles

2-6 Aliphatic diazonium coupling



$$Z{-}CH_2{-}Z' + ArN_2^+ \xrightarrow{OAc^-} Z{-}\overset{\displaystyle Z'}{\overset{|}{C}}{=}N{-}NHAr$$

If a C—H bond is acidic enough, it couples with diazonium salts in the presence of a base, most often aqueous sodium acetate.[49] The reaction is commonly carried out on compounds of the form $Z{-}CH_2{-}Z'$, where Z and Z′ are as defined on page 357, for example, β-keto esters, β-keto amides, malonic ester, nitroalkanes (in this case, only one Z is required), etc. However, certain compounds not of the form $Z{-}CH_2{-}Z'$ also give the reaction. Among these are conjugated dienes, where coupling takes place at the end of the conjugated system, and arylhydrazones, which give formazans:



$$CH_3{-}CH{=}N{-}NHPh + PhN_2^+ \longrightarrow CH_3{-}\underset{\displaystyle N{=}NPh}{\underset{|}{C}}{=}N{-}NHPh$$

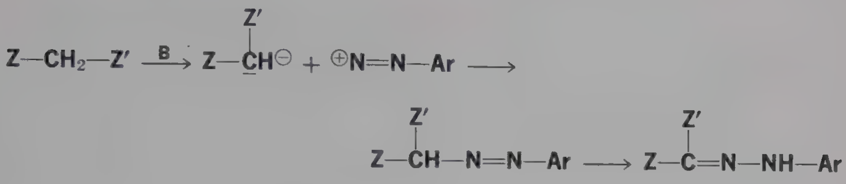
---

[47] For reviews, see Harwood, *Chem. Rev.* **62,** 99–154 (1962), pp. 102–103; Sonntag, *Chem. Rev.* **52,** 237–416 (1953), pp. 358–364.

[48] But see, however, Kwart and Scalzi, *J. Am. Chem. Soc.* **86,** 5496 (1964).

[49] For a review, see Parmerter, *Org. Reactions* **10,** 1–142 (1959).

The mechanism is probably of the simple S_E1 type:

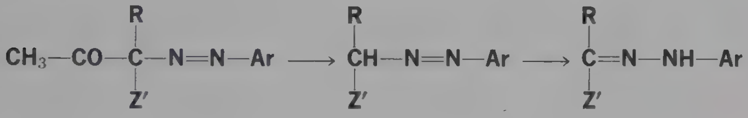


$$Z{-}CH_2{-}Z' \xrightarrow{B} Z{-}\overset{Z'}{\underline{C}}H^{\ominus} + {}^{\oplus}N{=}N{-}Ar \longrightarrow Z{-}\overset{Z'}{C}H{-}N{=}N{-}Ar \longrightarrow Z{-}\overset{Z'}{C}{=}N{-}NH{-}Ar$$

7 8

Aliphatic azo compounds which contain a hydrogen at the carbon containing the azo group (**7**) are unstable and tautomerize to the isomeric hydrazones (**8**), which are therefore the products of the reaction.

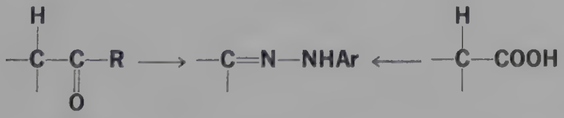
When the reaction is carried out on a compound of the form Z—CHR—Z′, so that the azo compound does not have a tautomerizable hydrogen, then if at least one Z is acyl or carboxyl, this group usually cleaves:



$$CH_3{-}CO{-}\overset{R}{\underset{Z'}{C}}{-}N{=}N{-}Ar \longrightarrow \overset{R}{\underset{Z'}{C}}H{-}N{=}N{-}Ar \longrightarrow \overset{R}{\underset{Z'}{C}}{=}N{-}NH{-}Ar$$

9

so that the product in this case too is the hydrazone, and not the azo compound. In fact, compounds of the type **9** are seldom isolable from the reaction, although this has been accomplished.[50] The cleavage step shown is actually an example of reaction **2-29** and, when a carboxyl group cleaves, of reaction **2-26.** The overall reaction in this case is called the *Japp-Klingemann reaction*[51] and involves conversion of a ketone (**10**) or an acid (**11**) to a hydrazone (**12**). When an acyl and a carboxyl group are both present, it is

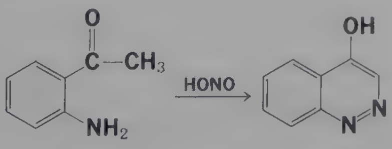


$$-\overset{H}{\underset{|}{C}}{-}\underset{O}{\overset{\|}{C}}{-}R \longrightarrow -\underset{|}{C}{=}N{-}NHAr \longleftarrow -\overset{H}{\underset{|}{C}}{-}COOH$$

10 12 11

the carboxyl which preferentially cleaves. When there is no acyl or carboxyl group present, then the aliphatic azo compound is stable (for example, the formazan shown above).

The reaction is occasionally used for ring closure:



---

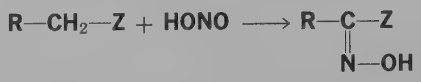
[50] See, for example, Yao and Resnick, *J. Am. Chem. Soc.* **84,** 3514 (1962).

[51] For a review, see Phillips, *Org. Reactions* **10,** 143–178 (1959).

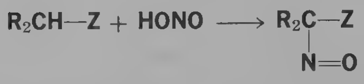
In this case the ketone first formed tautomerizes to give the aromatic ring.

OS **III,** 660; **IV,** 633.

2-7 Nitrosation at a carbon bearing an active hydrogen



$$\text{R—CH}_2\text{—Z} + \text{HONO} \longrightarrow \text{R—}\underset{\substack{\| \\ \text{N—OH}}}{\text{C}}\text{—Z}$$



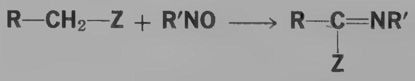
$$\text{R}_2\text{CH—Z} + \text{HONO} \longrightarrow \text{R}_2\underset{\substack{| \\ \text{N=O}}}{\text{C}}\text{—Z}$$

Carbons adjacent to a Z group (as defined on p. 357) may be nitrosated with nitrous acid or alkyl nitrites. The initial product is always the C-nitroso compound, but these are stable only when there is no tautomerizable hydrogen. When there is, the product is the more stable oxime. The situation is analogous to that with azo compounds and hydrazones (reaction **2-6**). The mechanism is similar to that in reaction **2-6:**

$$\text{R—H} \longrightarrow \text{R}^- + {}^+\text{N=O} \longrightarrow \text{R—N=O}$$

The attacking species is either NO$^+$ or a carrier of it. As in the Japp-Klingemann reaction, when Z is an acyl or carboxyl group (in the case of R$_2$CH—Z), it may be cleaved. Since oximes and nitroso compounds can be reduced to primary amines, this reaction often provides a route to amino acids.

Imines may be prepared in a similar manner, by treatment of an active hydrogen compound with a nitroso compound:

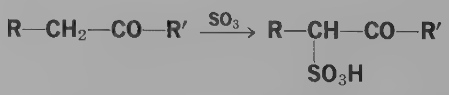


$$\text{R—CH}_2\text{—Z} + \text{R'NO} \longrightarrow \text{R—}\underset{\substack{| \\ \text{Z}}}{\text{C}}\text{=NR'}$$

OS **II,** 202, 204, 223, 363; **III,** 191, 513; **40,** 21. Also see OS **42,** 69.

D. Sulfur electrophiles

2-8 Sulfonation of aldehydes, ketones, and acids



$$\text{R—CH}_2\text{—CO—R'} \xrightarrow{\text{SO}_3} \text{R—}\underset{\substack{| \\ \text{SO}_3\text{H}}}{\text{CH}}\text{—CO—R'}$$

Aldehydes, ketones, and carboxylic acids containing α hydrogens can be sulfonated with sulfur trioxide.[52] The mechanism is presumably similar to that of reaction **2-4**. Sulfonation has also been accomplished at vinylic hydrogen.

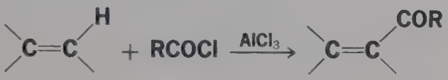
---

[52] For a review, see Gilbert, *Chem. Rev.* **62,** 549–589 (1962), pp. 558–559, and "Sulfonation and Related Reactions," pp. 33–61, Interscience Publishers, Inc., New York, 1965.

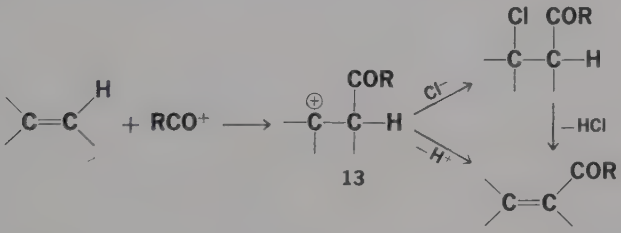
OS **IV**, 846, 862.

E. Carbon electrophiles. With respect to the attacking molecule, these are nucleophilic substitutions.

2-9 Acylation at an aliphatic carbon



Olefins can be acylated, in what is essentially a Friedel-Crafts reaction at an aliphatic carbon.[53] The product may arise by two paths. The initial attack is by the acyl cation RCO^+ (or by the acyl halide free or complexed, see reaction **1-14**, p. 413) on the olefin to give a carbonium ion:



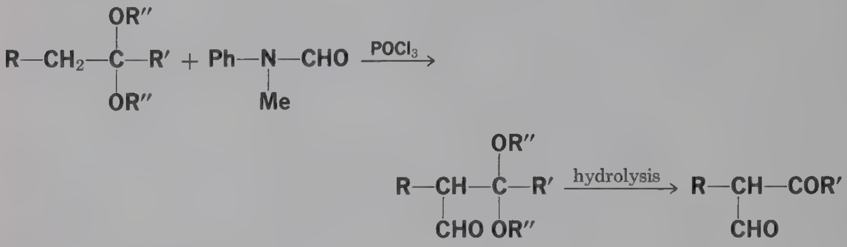
The carbonium ion (**13**) may either lose a proton or combine with chloride ion. If it loses a proton, the product is an unsaturated ketone, and the mechanism is S_E1. If it combines with chloride, the product is a β-halo ketone, which may be isolated, so that the result is addition to the double bond (see reaction **5-27**, p. 616). On the other hand, the β-halo ketone may, under the conditions of the reaction, lose HCl to give the unsaturated ketone, this time by an addition-elimination mechanism. In the case of unsymmetrical olefins, the attacking ion prefers the position at which there are more hydrogens, following Markovnikov's rule (p. 576). Anhydrides and acids are sometimes used instead of acyl halides. Even alkanes can be acylated with acyl halides and a Friedel-Crafts catalyst, if there is present a trace of a compound, such as an olefin, which can give rise to carbonium ions.

Formylation of olefins can be accomplished with N-disubstituted formamides and $POCl_3$.[54] This is an aliphatic Vilsmeier reaction (see reaction **1-18**, p. 417). Vilsmeier formylation may also be performed on the α position of acetals and ketals, so that hydrolysis of the products gives keto aldehydes or dialdehydes:[55]

---

[53] For reviews, see Nenitzescu and Balaban, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 1033–1152, Interscience Publishers, Inc., New York, 1964; and House, Ref. 40, pp. 282–287.

[54] For reviews, see Minkin and Dorofeenko, *Russ. Chem. Rev.* **29**, 599–618 (1960), pp. 606–608; and Olah and Kuhn, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 1214–1219, Interscience Publishers, Inc., New York, 1964.

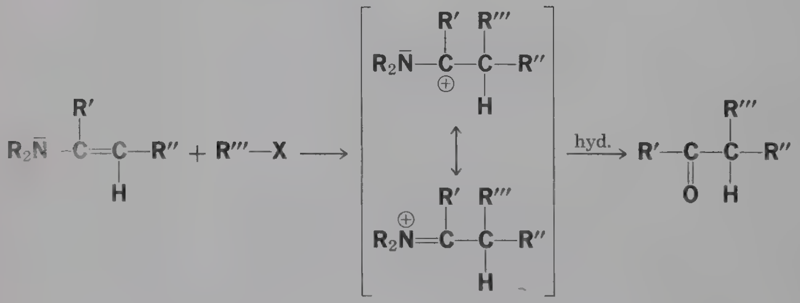


$$R{-}CH_2{-}\overset{OR''}{\underset{OR''}{C}}{-}R' + Ph{-}\underset{Me}{N}{-}CHO \xrightarrow{POCl_3} R{-}\underset{CHO}{CH}{-}\overset{OR''}{\underset{OR''}{C}}{-}R' \xrightarrow{\text{hydrolysis}} R{-}\underset{CHO}{CH}{-}COR'$$

Acetylation of acetals or ketals can be accomplished with acetic anhydride and BF_3-etherate.[56] The mechanism with acetals or ketals also involves attack at an olefinic carbon, since enol ethers are intermediates.[56] Ketones can be formylated in the α position by treatment with CO and a strong base.[57]

OS **IV,** 555, 560.

2-10 The Stork enamine reaction



$$R_2\bar{N}{-}\overset{R'}{C}{=}\underset{H}{C}{-}R'' + R'''{-}X \longrightarrow \left[R_2\bar{N}{-}\overset{R'}{\underset{\oplus}{C}}{-}\overset{R'''}{\underset{H}{C}}{-}R'' \longleftrightarrow R_2\overset{\oplus}{N}{=}\overset{R'}{C}{-}\overset{R'''}{\underset{H}{C}}{-}R'' \right] \xrightarrow{\text{hyd.}} R'{-}\underset{\underset{O}{\|}}{C}{-}\overset{R'''}{\underset{H}{C}}{-}R''$$

When enamines are treated with alkyl halides, an alkylation occurs which is analogous to the first step of reaction **2-9.** Hydrolysis of the imine salt gives a ketone. Since the enamine is normally formed from a ketone (reaction **6-15,** p. 667), the net result is alkylation of the ketone at the α position. The method is known as the *Stork enamine reaction*[58] and represents an alternative to the ketone alkylation considered at reaction **0-86** (p. 357). The Stork method has the advantage that it leads to monoalkylation of the ketone, while reaction **0-87,** when applied to ketones, is difficult to stop with the introduction of just one alkyl group. Alkylation usually takes place on the less substituted side of the original ketone.

---

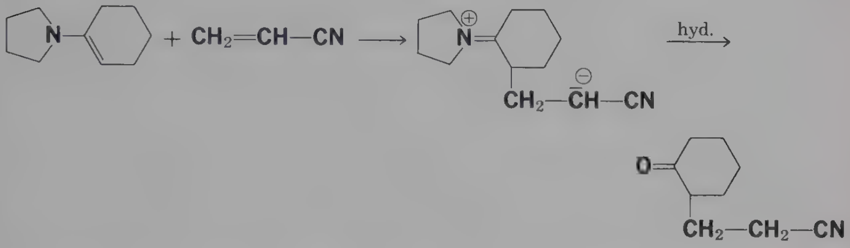
[55] Youssefyeh, *Tetrahedron Letters* **1964,** 2161.

[56] Youssefyeh, *J. Am. Chem. Soc.* **85,** 3901 (1963).

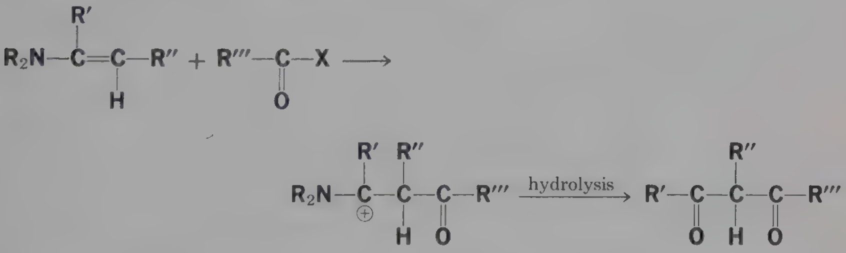
[57] See, for example, van der Zeeuw and Gersmann, *Rec. trav. chim.* **84,** 1535 (1965).

[58] Stork, Brizzolara, Landesman, Szmuszkovicz, and Terrell, *J. Am. Chem. Soc.* **85,** 207 (1963); for reviews, see Szmuszkovicz, *Advan. Org. Chem.* **4,** 1–113 (1963), pp. 25–92; and House, Ref. 40, pp. 197–204, 274–276.

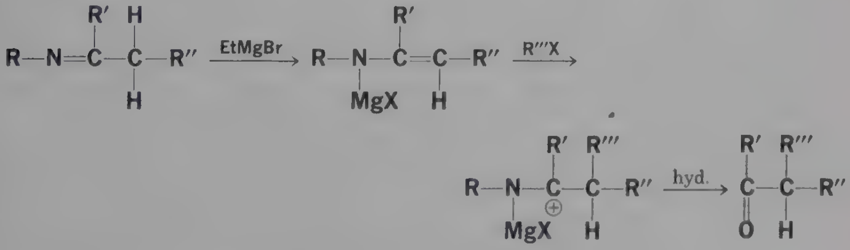
The method is quite useful for particularly active alkyl halides, such as allyl, benzyl, and propargyl halides, and for α-halo ethers and esters but is not very serviceable for ordinary primary and secondary halides. Tertiary halides do not give the reaction at all, since with respect to the halide this is nucleophilic substitution, and elimination predominates. The reaction may also be applied to activated aryl halides (such as 2,4-dinitrochlorobenzene; see Chapter 13), and to activated olefins, such as acrylonitrile, e.g.,



The latter is a Michael-type reaction (p. 568) with respect to the olefin. Acylation can be accomplished with acyl halides:



Primary and secondary halides do not perform well, mostly because N-alkylation becomes important, particularly with enamines derived from aldehydes. An alternative method, which does give good yields of alkylation with primary and secondary halides, is alkylation of enamine *salts*, which are prepared by treating an imine with ethylmagnesium bromide in tetrahydrofuran:[59]



The imines are prepared by reaction **6-15,** p. 667.

OS **43,** 34; **45,** 80.

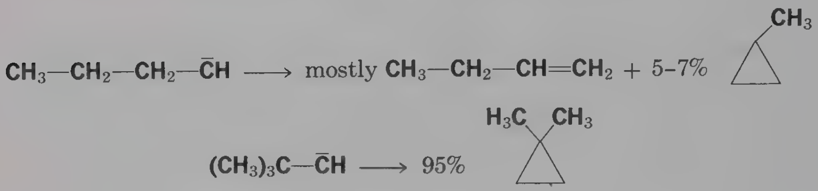
---

[59] Stork and Dowd, *J. Am. Chem. Soc.* **85,** 2178 (1963).

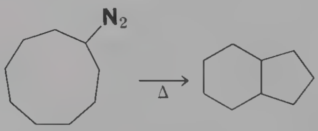
2-11 Insertion by carbenes

$$RH + \bar{C}H_2 \longrightarrow RCH_3$$

The highly reactive species carbene inserts into C—H bonds,[60] both aliphatic and aromatic,[61] although with aromatic compounds ring expansion is also possible (see reaction **5-37**, p. 643). The reaction is useless for synthetic purposes because of its nonselectivity (see p. 164). Alkylcarbenes usually rearrange rather than give insertion (p. 165), but when this is impossible, *intramolecular* insertion is found, rather than intermolecular:[62]



Transannular insertion is also known:[63]



CH_2 generated by photolysis of CH_2N_2 in the liquid phase is indiscriminate—totally nonselective—in its reactivity (p. 164). CH_2 generated in other ways, and other carbenes, are less reactive and insert in the order tertiary > secondary > primary.[64] Halocarbenes insert much less readily, and only a few instances have been reported.[65] Nevertheless, even for less reactive carbenes, the insertion reaction has not been used for synthetic purposes. The carbenes may be generated in any of the ways mentioned in Chapter 5 (p. 162). Carbon atoms (which may be considered a type of carbene) also insert into C—H bonds. The reaction between carbon atoms and isobutane gave 1,1-dimethylcyclopropane (**14**), 2-methylbutane (**15**), and octanes, which were presumed to arise in this manner:[66]

---

[60] First reported by Meerwein, Rathjen, and Werner, *Ber.* **75**, 1610 (1942). For reviews, see Hine, "Divalent Carbon," pp. 15–20, 110–116, The Ronald Press Company, New York, 1964; Kirmse, "Carbene Chemistry," pp. 21–26, 52–64, 251–258, Academic Press Inc., New York, 1964; and Bell, *Progr. Phys. Org. Chem.* **2**, 1–61 (1964), pp. 30–43.

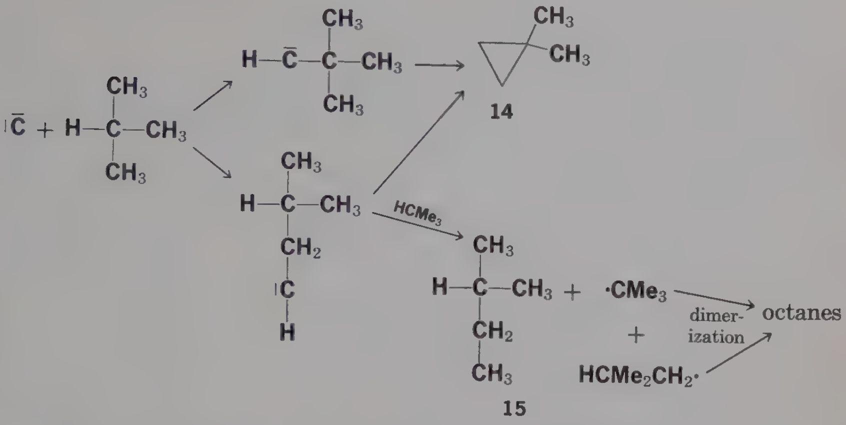
[61] Terao and Shida, *Bull. Chem. Soc. Japan* **37**, 687 (1964).

[62] Kirmse and Doering, *Tetrahedron* **11**, 266 (1960); Friedman and Berger, *J. Am. Chem. Soc.* **83**, 492, 500 (1961). Also see Kirmse and Wächtershäuser, *Tetrahedron* **22**, 63, 73 (1966).

[63] Friedman and Shechter, *J. Am. Chem. Soc.* **83**, 3159 (1961).

[64] Doering and Knox, *J. Am. Chem. Soc.* **83**, 1989 (1961).

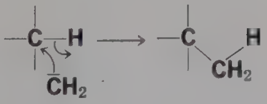
[65] Parham and Koncos, *J. Am. Chem. Soc.* **83**, 4034 (1961); Fields, *J. Am. Chem. Soc.* **84**, 1744 (1962); Anderson, Lindsay, and Reese, *J. Chem. Soc.* **1964**, 4874; Seyferth and Burlitch, *J. Am. Chem. Soc.* **85**, 2667 (1963); Seyferth and Washburne, *J. Organometal. Chem.* **5**, 389 (1966).



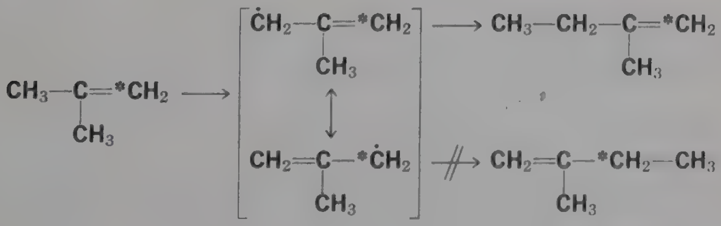
Nitrenes have also been found to insert into C—H bonds.[67]

The mechanism of the insertion reaction is not known with certainty, but there seem to be at least two possible pathways.

1. A simple simultaneous process:



The most convincing evidence for this mechanism is that in the reaction between 1-^{14}C-isobutylene and carbene, the product, 2-methyl-1-butene, was labeled only in the 1-position.[68] This rules out a free radical or other free intermediate such as a carbonium ion or carbanion. If **16** (or a corresponding ion) were an intermediate, then resonance would ensure that some carbene attacked at the 1-position:



---

[66] Engel and Skell, *J. Am. Chem. Soc.* **87**, 4663 (1965).
[67] Smolinsky and Feuer, *J. Am. Chem. Soc.* **86**, 3085 (1964).
[68] Doering and Prinzbach, *Tetrahedron* **6**, 24 (1959).

2. A free-radical process:

$$RH + \bar{C}H_2 \longrightarrow R\cdot + CH_3\cdot$$
$$R\cdot + CH_3\cdot \longrightarrow RCH_3$$

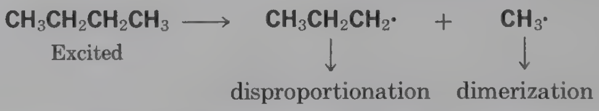
One fact supporting this mechanism is that among the products obtained (besides butane and isobutane) upon treatment of propane with CH_2 (generated by photolysis of diazomethane and ketene) were propene and ethane,[69] which could arise, respectively, by

$$2CH_3CH_2CH_2\cdot \longrightarrow CH_3CH{=}CH_2 + CH_3CH_2CH_3 \qquad \text{(disproportionation)}$$

and

$$CH_3CH_2CH_3 + \bar{C}H_2 \longrightarrow CH_3CH_2CH_2\cdot + CH_3\cdot$$
$$2CH_3\cdot \longrightarrow CH_3CH_3$$

Of course, this does not necessarily mean that the free-radical process is the *only* mechanism operating under these conditions, assuming that it operates at all. The obtention of these products has also been explained in a different manner.[70] We have seen that the product of the reaction between a carbene and a molecule may have excess energy (p. 161). Therefore it is possible that CH_2 and propane react by the simultaneous mechanism, and the excess energy causes the butane thus formed to cleave to free radicals:



$$\underset{\text{Excited}}{CH_3CH_2CH_2CH_3} \longrightarrow \underset{\text{disproportionation}}{\underset{\downarrow}{CH_3CH_2CH_2\cdot}} + \underset{\text{dimerization}}{\underset{\downarrow}{CH_3\cdot}}$$

According to this explanation, the free radicals are formed *after* the actual insertion reaction.

The reaction in which aldehydes are converted to methyl ketones, $RCHO + CH_2N_2 \rightarrow RCOCH_3$, while apparently similar, does not involve a free carbene intermediate. It will be considered in Chapter 18 (reaction **8-9**, p. 810).

F. Metal electrophiles

2-12 Metalation with organometallic compounds

$$RH + R'M \longrightarrow RM + R'H$$

Many organic compounds can be metalated by treatment with an organometallic compound.[71] Since the reaction involves a proton transfer, the equilibrium lies on the side of the weaker acid. For example, fluorene reacts with butyllithium to give butane and 9-fluoryllithium. Since aromatic hydrocarbons are usually stronger acids than aliphatic ones, R is most often aryl. The most common reagent is butyllithium. However, benzene itself gives little or no reaction when treated with butyllithium, which reacts only with active aromatic rings. Metalation of aliphatic RH is most successful when the carbanions are stabilized by resonance (allyl, benzyl, etc.) or when the negative charge is at an *sp* carbon (at triple bonds).

---

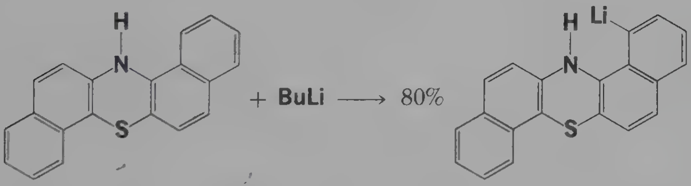
[69] Frey, *Proc. Chem. Soc.* **1959**, 318.

[70] Bell, Ref. 60.

[71] For reviews, see Jones and Gilman, *Chem. Rev.* **54**, 835–890 (1954), pp. 865–867; Gilman and Morton, *Org. Reactions* **8**, 258–304 (1954) (for Li); Benkeser, Foster, Sauve, and Nobis, *Chem. Rev.* **57**, 867–894 (1957) (for Na). Also see Ref. 78.

In general the reaction can be performed only with organometallics of active metals such as lithium, sodium, and potassium, but Grignard reagents abstract protons from a sufficiently acidic C—H bond, as in $R-C\equiv C-H \longrightarrow R-C\equiv C-MgX$. This is the best method for the preparation of ethynyl Grignard reagents.

The reaction may be used to determine relative acidities of very weak acids, by allowing two R—H compounds to compete for the same R′M; and to determine which proton in a molecule is the most acidic. The reaction is often remarkably specific, for example,[72]



The mechanism involves a nucleophilic attack by R'^- (or a polar R′) on the *hydrogen.*[73] Evidence for this is that mesomeric effects of substituents in R seem to make little difference. Only inductive effects are important. When R is aryl, OMe and CF_3 *both* direct ortho, while isopropyl directs meta and para (mostly meta).[74] These results are exactly what would be expected from pure inductive effects, with no contribution from resonance effects. All this implies that attack occurs at the hydrogen and not at R. Only the acidity seems to be important. Resonance factors would influence an intermediate or transition state. Since resonance factors in R are not important, R is involved very little in the transition state. Other evidence for the involvement of H in the rate-determining step is that there is an isotope effect.[75] The nature of R′ also has an effect on the rate. In the reaction between triphenylmethane and R′Li, the rate decreased in the order $R' = PhCH_2 >$ allyl $>$ Bu $>$ Ph $>$ vinyl $>$ Me.[76]

With respect to the reagent, this reaction is a special case of reaction **2-14.**

---

[72] Shirley and Gilmer, *J. Org. Chem.* **27,** 4421 (1962). For other uses of this reaction to determine position of maximum acidity, see Broaddus, Logan, and Flautt, *J. Org. Chem.* **28,** 1174 (1963); Finnegan and McNees, *J. Org. Chem.* **29,** 3234 (1964).

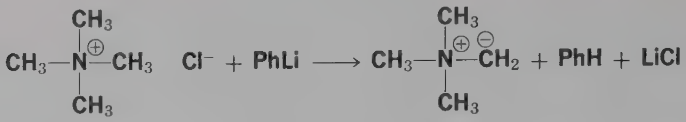
[73] Benkeser, Trevillyan, and Hooz, *J. Am. Chem. Soc.* **84,** 4971 (1962).

[74] Bryce-Smith, *J. Chem. Soc.* **1963,** 5983; Benkeser, Hooz, Liston, and Trevillyan, *J. Am. Chem. Soc.* **85,** 3984 (1963).

[75] Bryce-Smith, Gold, and Satchell, *J. Chem. Soc.* **1954,** 2743.

[76] Waack and West, *J. Am. Chem. Soc.* **86,** 4494 (1964).

A closely related reaction is formation of nitrogen ylides from quaternary ammonium salts (see reaction **7-7,** p. 761):



$$\mathrm{CH_3{-}\overset{CH_3}{\underset{CH_3}{N^{\oplus}}}{-}CH_3\ \ Cl^- + PhLi \longrightarrow CH_3{-}\overset{CH_3}{\underset{CH_3}{N^{\oplus}}}{-}\overset{\ominus}{C}H_2 + PhH + LiCl}$$

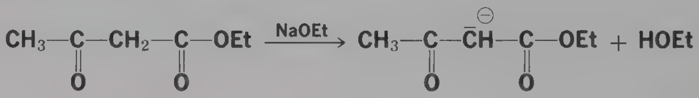
Phosphonium salts undergo a similar reaction (see reaction **6-45,** p. 702).

OS **II,** 198; **III,** 413, 757; **IV,** 792; **40,** 66.

2-13 Metalation with metals and strong bases

$$\mathrm{2RH + M \longrightarrow 2RM + H_2}$$

Organic compounds may be metalated at suitably acidic positions by active metals and strong bases. The reaction has been used to study the acidities of very weak acids (see p. 143). Synthetically, the most important use of the method is to convert activated ketones, esters, and similar compounds to their enolate forms, e.g.,



$$\mathrm{CH_3{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}OEt \xrightarrow{NaOEt} CH_3{-}\underset{\underset{O}{\|}}{C}{-}\overset{\ominus}{C}H{-}\underset{\underset{O}{\|}}{C}{-}OEt + HOEt}$$

for use in nucleophilic substitutions (reactions **0-86,** p. 357, and **3-14,** p. 506) and in additions to multiple bonds (reactions **5-15,** p. 604, and **6-41,** p. 697). The mechanism for the reaction between $\mathrm{ArCR_2H}$ and RNHLi has been shown to be $\mathrm{S_Ei}$.[77]

OS **IV,** 473; **41,** 96. We do not list conversions of ketones or esters to enolates.

Metals as Leaving Groups

A. Hydrogen as the electrophile

2-14 Replacement of metals by hydrogen

$$\mathrm{RM + HA \longrightarrow RH + MA}$$

Organometallic compounds react with acids in reactions in which the metal is replaced by hydrogen.[78] R may be aryl (see reaction **1-47,** p. 440). For Grignard reagents, water is usually a strong enough acid, but stronger acids are also used. Hydrogen (H_2) has been used as an acid, to convert Grignard reagents to hydrocarbons.[79] An important method for the reduction of alkyl halides consists of the process

---

[77] Streitwieser, Van Sickle, and Langworthy, *J. Am. Chem. Soc.* **84,** 244 (1962); Streitwieser and Langworthy, *J. Am. Chem. Soc.* **84,** 249 (1962); Streitwieser, Langworthy, and Van Sickle, *J. Am. Chem. Soc.* **84,** 251 (1962); Streitwieser and Van Sickle, *J. Am. Chem. Soc.* **84,** 254 (1962); Streitwieser and Reif, *J. Am. Chem. Soc.* **84,** 258 (1962).

[78] For reviews, see Rochow, Hurd, and Lewis, "The Chemistry of Organometallic Compounds," John Wiley & Sons, Inc., New York, 1957; Coates, "Organometallic Compounds," 2d ed., John Wiley & Sons, Inc., New York, 1960; Schlosser, *Angew. Chem. Intern. Ed. Engl.* **3,** 287, 362 (1964) (for sodium and potassium).

$$\mathrm{RX} \longrightarrow \mathrm{RMgX} \longrightarrow \mathrm{RH}$$

Other organometallic compounds that are hydrolyzed by water are those of sodium, potassium, lithium, zinc, etc.: the ones high in the electromotive series. When the metal is farther down in the series, stronger acids are required. For example, R_2Zn compounds react explosively with water, R_2Cd slowly, and R_2Hg not at all, though the latter may be cleaved with concentrated HCl. However, this general statement has many exceptions, some hard to explain. For example, BR_3 compounds are completely inert to water, and GaR_3 types at room temperature cleave just one R group, but AlR_3 react violently with water. However, BR_3 may be converted to RH with carboxylic acids.[80] For less active metals it is often possible to cleave just one R group from a multivalent metal. For example,

$$\mathrm{R_2Hg + HCl \longrightarrow RH + RHgCl}$$

Organometallic compounds of less active metals and metalloids, such as silicon, antimony, bismuth, etc., are quite inert to water. Organomercury compounds (RHgX) may be reduced to RH by treatment with $NaBH_4$ in aqueous basic solution.[81]

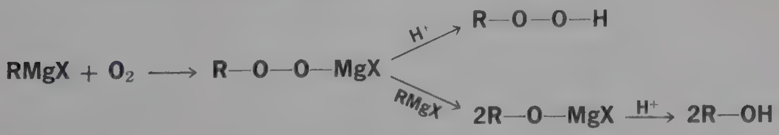
In the *Zerewittenoff* process the number of moles of active hydrogen in an unknown compound is determined by treatment of the compound with methylmagnesium bromide and measurement of the volume of methane evolved. An *active hydrogen* is defined as one which will react with this reagent. Usually it is a hydrogen connected to oxygen, nitrogen, sulfur, phosphorus, etc., but hydrogen attached to some carbons are acidic enough for the reaction.[82]

When the hydrogen of the HA is attached to carbon, this reaction is the same as reaction **2-12.**

We do not list the many hydrolyses of sodium or potassium enolates, etc., which are found in *Organic Syntheses.* The hydrolysis of a Grignard reagent to give an alkane is found at OS **II,** 478.

B. Oxygen electrophiles

2-15 The reaction between Grignard reagents and oxygen



---

[79] Becker and Ashby, *J. Org. Chem.* **29,** 954 (1964).

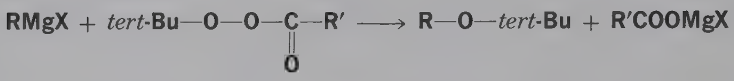
[80] Brown, "Hydroboration," pp. 64–65, W. A. Benjamin, Inc., New York, 1962.

[81] Bordwell and Douglass, *J. Am. Chem. Soc.* **88,** 993 (1966).

[82] For a review, see Kharasch and Reinmuth, "Grignard Reactions of Nonmetallic Substances," pp. 1166–1198, Prentice-Hall, Inc., Englewood Cliffs, N.J., 1954.

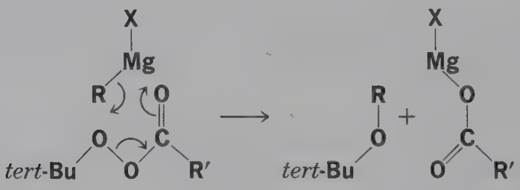
Oxygen reacts with Grignard reagents to give either hydroperoxides or alcohols.[83] The reaction is useful to convert alkyl halides to alcohols without side reactions. With aryl Grignard reagents yields are lower, and only phenols are obtained, not hydroperoxides. It is because of the possibility of this reaction that oxygen must be excluded when Grignard reagents are desired for other purposes. Most other organometallic compounds also react with oxygen, though a few, notably organomercury compounds, do not.

2-16 Conversion of Grignard reagents to *tert*-butyl ethers



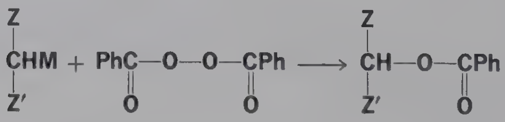
$$\mathrm{RMgX} + tert\text{-}\mathrm{Bu{-}O{-}O{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R'} \longrightarrow \mathrm{R{-}O{-}}tert\text{-}\mathrm{Bu} + \mathrm{R'COOMgX}$$

A convenient method of preparation of *tert*-butyl ethers consists of treating Grignard reagents with *tert*-butyl acyl peroxides.[84] Both alkyl and aryl Grignard reagents may be used. The mechanism is probably of the cyclic six-centered type:



OS **41,** 91; **43,** 55.

2-17 Esterification of enolates



$$\mathrm{Z{-}\underset{\underset{\displaystyle Z'}{|}}{C}HM} + \mathrm{Ph\underset{\underset{\displaystyle O}{\|}}{C}{-}O{-}O{-}\underset{\underset{\displaystyle O}{\|}}{C}Ph} \longrightarrow \mathrm{Z{-}\underset{\underset{\displaystyle Z'}{|}}{C}H{-}O{-}\underset{\underset{\displaystyle O}{\|}}{C}Ph}$$

β-Keto esters and other compounds of the form Z—CHR—Z′ (see p. 357 for the definition of Z) may be esterified through their enolate salts, by treatment with acyl peroxides.[85]

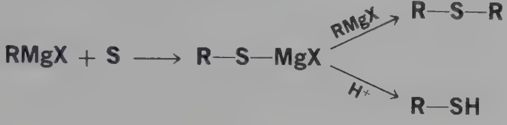
[83] For a review, see Ref. 82, pp. 1264–1274.

[84] Lawesson and Yang, *J. Am. Chem. Soc.* **81,** 4230 (1959); Jakobsen, Larsen, and Lawesson, *Rec. trav. chim.* **82,** 791 (1963); Lawesson and Frisell, *Arkiv Kemi* **17,** 393 (1961); Lawesson, Frisell, Denney, and Denney, *Tetrahedron* **19,** 1229 (1963).

[85] Lawesson and Frisell, *Arkiv Kemi* **17,** 409 (1961); Lawesson, Andersson, and Berglund, *Arkiv Kemi* **17,** 429 (1961); Lawesson, Jönsson, and Taipale, *Arkiv Kemi* **17,** 441 (1961); Lawesson, Grönwall, and Andersson, *Arkiv Kemi* **17,** 457 (1961).

C. Sulfur electrophiles

2-18 Conversion of Grignard reagents to mercaptans and sulfides



Mercaptans and sulfides are occasionally prepared by treatment of Grignard reagents with sulfur. Analogous reactions are known for selenium and tellurium compounds.

OS **III,** 771; **IV,** 667.

D. Halogen electrophiles

2-19 Halogenation of Grignard reagents

$$\mathrm{RMgX} + \mathrm{I_2} \longrightarrow \mathrm{RI} + \mathrm{MgIX}$$

Grignard reagents react with halogens to give alkyl halides. The reaction represents a useful method for the preparation of iodo compounds from the corresponding chloro or bromo compounds. Most organometallic compounds, both alkyl and aryl, behave similarly. It has been shown that the reaction between RHgX and Br_2 may sometimes involve a free-radical mechanism.[86]

OS **I,** 125, 325, 326; **III,** 774, 813. Also see OS **II,** 150.

E. Metal electrophiles

2-20 Replacement of a metal with a metal

$$\mathrm{RM} + \mathrm{M'} \rightleftharpoons \mathrm{RM'} + \mathrm{M}$$

Many organometallic compounds are best prepared by this reaction, which involves replacement of a metal in an organometallic compound by another metal.[87] RM′ can be successfully prepared only when M′ is above M in the electromotive series, unless some other way is found to shift the equilibrium. That is, RM is usually an unreactive compound, and M′ a metal more active than M. Most often, RM is R_2Hg, since mercury alkyls are easy to prepare, and mercury is far down in the electromotive series. Alkyls of Li, Na, Be, Mg, Al, Ga, Zn, Cd, Te, Sn, etc., have been prepared in this way. An important advantage of this method over reaction **2-24** is that it ensures that the organometallic compound will be prepared free of any possible halide. This is the only practical method for the *isolation* of solid sodium and potassium alkyls. If the metals lie too close together in the series, it may not be possible to shift the equilibrium. For example, alkylbismuth compounds cannot be prepared in this way from alkylmercury compounds.

---

[86] Beletskaya, Reutov, and Gur'yanova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1961,** 1483; Beletskaya, Reutov, and Azizyan, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1962,** 204; Beletskaya, Ermanson, and Reutov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1965,** 218.

[87] For a review, see Jones and Gilman, *Chem. Rev.* **54,** 835–890 (1954), pp. 841–845.

OS **45,** 107.

2-21 Replacement of a metal with a metal halide

$$RM + M'X \rightleftharpoons RM' + MX$$

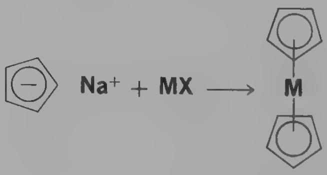
In contrast to reaction **2-20,** the reaction between an organometallic compound and a metal *halide* is successful only when M′ is *below* M in the electromotive series.[88] The two reactions considered together therefore constitute a powerful tool for preparing all kinds of organometallic compounds. In this reaction the most common substrates are Grignard reagents. Among others, alkyls of Be, Zn, Cd, Hg, Al, Sn, Pb, Co, Pt, and Au have been prepared by treatment of Grignard reagents with the appropriate halide. The reaction has been used to prepare alkyls of almost all nontransition metals and even of some transition metals. Alkyls of metalloids and of nonmetals, including Si, B, Ge, P, As, Sb, and Bi, can also be prepared in this manner.[89] Except for alkali-metal alkyls and Grignard reagents, the reaction between RM and M′X is the most common method for the preparation of organometallic compounds.

If M′ has a valence higher than 1, it is often possible to stop the reaction before all the halogens have been replaced, e.g.,

$$RMgX + SiCl_4 \longrightarrow RSiCl_3$$

However, it is not always possible: $RMgX + BF_3$ gives only BR_3, although $BRCl_2$ can be prepared from R_2Zn and BCl_3.

Metallocenes (see p. 42) are usually made by this method:



Among others, metallocenes of Sc, Ti, V, Cr, Mn, Fe, Co, and Ni have been prepared in this manner.[90]

Metal nitrates are sometimes used instead of halides. For example, silver alkyls have been prepared from alkyllead compounds and silver nitrate.[91]

OS **I,** 231, 550; **III,** 601; **IV,** 258, 473, 881; **41,** 96; **46,** 65. Also see OS **IV,** 476.

---

[88] For a review, see Ref. 87, pp. 847–856. Also see Ref. 78.

[89] For a review as applied to Si, B, and P, see Ref. 82, pp. 1306–1345.

[90] For a review, see Birmingham, *Advan. Organometal. Chem.* **2,** 365–413 (1965), pp. 375–382.

[91] Brown, Hérbert, and Snyder, *J. Am. Chem. Soc.* **83,** 1001 (1961).

2-22 Replacement of a metal with an organometallic compound

$$\mathrm{RM} + \mathrm{R'M'} \rightleftharpoons \mathrm{RM'} + \mathrm{R'M}$$

This type of metallic exchange is used much less often than reactions **2-20** and **2-21**. It is an equilibrium reaction and is useful only if the equilibrium lies in the desired direction. Usually the goal is to prepare a lithium compound which is not prepared easily in other ways, for example, vinyl- or allyllithium.[92] An example is the preparation of vinyllithium from phenyllithium and tin tetravinyl. The reaction proceeds with retention of configuration;[93] an S_Ei mechanism is likely.[94]

OS **41**, 30.

Halogen as Leaving Group

A. Hydrogen as the electrophile

2-23 Reduction of alkyl halides. Although this reaction can proceed by an electrophilic substitution mechanism, it is considered in Chapter 10 (reaction **0-73**, p. 348).

B. Metal electrophiles

2-24 Replacement of a halogen with a metal

$$\mathrm{RX} + \mathrm{M} \longrightarrow \mathrm{RM}$$

Alkyl halides react directly with certain metals to give organometallic compounds. The most common metal is magnesium, and, of course, this is by far the most common method for the preparation of Grignard reagents.[95] The order of halide activity is I > Br > Cl. The reaction may be applied to many alkyl halides—primary, secondary, and tertiary—and to aryl halides, although aryl *chlorides* require the use of tetrahydrofuran or another higher-boiling solvent instead of the usual ether, or the use of special entrainment methods.[96] Aryl iodides and bromides may be treated in the usual manner. Special conditions must be employed for particularly reactive halides such as allyl, since these under ordinary conditions produce Wurtz-type coupling (see reaction **0-81**, p. 353). Vinyl halides also require higher-boiling solvents (see OS **IV**, 258) and ethynyl Grignard reagents cannot be prepared by this method at all. For these, reaction **2-12** is used. Dihalides can be converted to Grignard reagents if the halogens are different and are at least three carbons apart. 1,2-Dihalides give elimination instead of Grignard reagent formation (reaction **7-22**, p. 770), and the reaction is seldom successful with 1,1-dihalides, although it has been accomplished.[97]

---

[92] For reviews, see Seyferth, Vaughan, Raab, Welch, Cohen, and Alleston, *Bull. Soc. chim. France* **1963**, 1364–1367; and Ref. 87, pp. 863–865.

[93] Seyferth and Vaughan, *J. Am. Chem. Soc.* **86**, 883 (1964).

[94] Dessy, Kaplan, Coe, and Salinger, *J. Am. Chem. Soc.* **85**, 1191 (1963).

[95] For reviews, see Ref. 82, pp. 5–91; Ref. 87, pp. 836–841.

[96] Pearson, Cowan, and Beckler, *J. Org. Chem.* **24**, 504 (1959).

The presence of other functional groups in the halide usually affects the preparation of the Grignard reagent. Groups which contain active hydrogen (as defined on p. 471), such as OH, NH_2, and COOH, may be present in the molecule, but only if they are converted to the salt form (O^-, NH^-, COO^-, respectively). Some groups, such as nitro, inhibit formation of the Grignard reagent entirely. On the other hand, OR and NR_2 groups usually have no effect on Grignard reagent formation.

Grignard reagents may also be prepared in benzene or toluene, if a tertiary amine is added to complex with the RMgX.[98] This method eliminates the need for an ether solvent.

The reaction has also been carried out with many other metals, e.g., Li, Na, Be, Zn, Hg, As, Sb, and Sn,[99] but it is not applicable to transition metals. With sodium, the Wurtz reaction (**0-81**, p. 353) is an important side reaction. The reaction is not successful for potassium, complex mixtures being obtained in which RK is an unimportant constituent.[100] In some cases where the reaction between a halide and a metal is too slow, an alloy of the metal with potassium or sodium can be used instead. The most important example is the preparation of lead tetraethyl from ethyl bromide and a Pb-Na alloy.

The mechanism of Grignard reagent formation is not well known, though much work has been done in this area. It may not even be electrophilic substitution. The reaction between alkyl halides and lithium probably proceeds by an S_Ei mechanism.[101]

There are too many preparations of Grignard reagents in *Organic Syntheses* for us to list here. Use of the reaction to prepare other organometallic compounds will be found in OS **I,** 228; **II,** 184, 517, 607; **III,** 413, 757.

2-25 Replacement of a halogen by a metal from an organometallic compound

$$RX + R'M \longrightarrow RM + R'X$$

The exchange reaction between alkyl halides and organometallic compounds is almost entirely limited to the cases where M is lithium and X is bromide or iodide,[102] though it has been shown to occur with magnesium.[103] R′ is usually, though not always, alkyl, and often butyl; R is usually aromatic. Of course, the R which becomes bonded to the halogen is the one for which RH is the weaker acid. The mechanism when both R and R′ are aryl has been formulated:[104]

$$(ArLi)_2 + Ar'Br \rightleftharpoons (ArLiLiAr') + ArBr$$

$$(ArLiLiAr') + Ar'Br \rightleftharpoons (Ar'Li)_2 + ArBr$$

---

[97] For a review of the preparation of Grignard reagents from dihalides, see Millar and Heaney, *Quart. Rev.* (*London*) **11,** 109–120 (1957).

[98] Ashby and Reed, *J. Org. Chem.* **31,** 971 (1966).

[99] For a review, see Rochow, *J. Chem. Educ.* **43,** 58–62 (1966).

[100] Finnegan, *Tetrahedron Letters* **1962,** 1303, **1963,** 851.

[101] Walborsky and Young, *J. Am. Chem. Soc.* **86,** 3288 (1964).

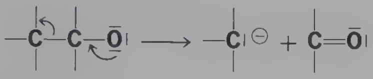
[102] For reviews, see Jones and Gilman, *Org. Reactions* **6,** 339–366 (1951); and Ref. 87, pp. 867–868.

[103] Zakharkin, Okhlobystin, and Bilevitch, *J. Organometal. Chem.* **2,** 309 (1964).

[104] Winkler and Winkler, *J. Am. Chem. Soc.* **88,** 964, 969 (1966).

Carbon Leaving Groups. In these reactions (**2-26** to **2-32**) a carbon-carbon bond cleaves.[105] We regard as the substrate that side which retains the electron pair; hence the reactions are considered to be electrophilic substitutions. The incoming group is hydrogen in all but one (reaction **2-28**) of the cases. These reactions are sometimes called *anionic cleavages,* though they do not always occur by mechanisms involving free carbanions (S_E1). When they do, the reactions are facilitated by increasing stability of the carbanion.

A. Carbonyl-forming cleavages. These reactions follow the pattern

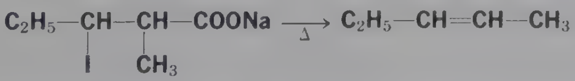


The leaving group is stabilized because the electron deficiency at its carbon is satisfied by a pair of electrons from the oxygen. With respect to the leaving group the reaction is elimination to form a C=O bond. Retrograde aldol condensations (reaction **6-39,** p. 692) and cleavage of cyanohydrins (reaction **6-47,** p. 710) belong to this classification but are treated in Chapter 6, under their more important reverse reactions. Other eliminations to form C=O bonds are discussed in Chapter 7 (reactions **7-34** to **7-36,** pp. 778–779).

2-26 Decarboxylation of aliphatic acids

$$RCOOH \longrightarrow RH + CO_2$$

Many carboxylic acids can be successfully decarboxylated, either as the free acid or in the salt form, but not simple fatty acids.[106] An exception is acetic acid, which as the acetate, heated with base, gives good yields of methane. Aliphatic acids which do undergo successful decarboxylation have certain functional groups or double or triple bonds in the α or β positions. Some of these are shown in Table 1. For decarboxylation of aromatic acids, see reaction **1-40** (p. 435). Decarboxylation of an α-cyano acid may give a nitrile or a carboxylic acid, since the cyano group may or may not be hydrolyzed in the course of the reaction. In addition to the compounds listed in Table 1, decarboxylation can also be carried out on α,β-olefinic and -acetylenic acids, acids with a positive sulfur in the α position, for example, $Me_2\overset{+}{S}CH_2COOH$ Br^-,[107] and certain acids with a positive nitrogen in the α position.[108] β-Halo acids give decarboxylation accompanied by elimination:[109]



$$C_2H_5-\underset{\displaystyle I}{CH}-\underset{\displaystyle CH_3}{CH}-COONa \xrightarrow[\Delta]{} C_2H_5-CH=CH-CH_3$$

---

[105] For a review, see Shemyakin and Shchukina, *Quart. Rev.* (*London*) **10,** 261–282 (1956).

[106] March, *J. Chem. Educ.* **40,** 212 (1963).

[107] Burness, *J. Org. Chem.* **24,** 849 (1959).

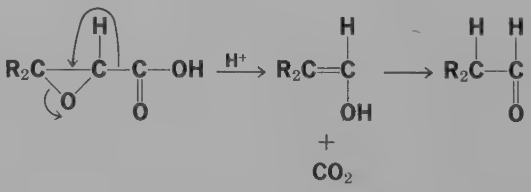
[108] Haake and Mantecon, *J. Am. Chem. Soc.* **86,** 5230 (1964).

[109] Lucas and Prater, *J. Am. Chem. Soc.* **59,** 1684 (1937).

TABLE 1. Some acids which undergo decarboxylation fairly readily Others are described in the text

	Acid type	*Decarboxylation product*
Malonic	$HOOC-\overset{\vert}{\underset{\vert}{C}}-COOH$	$HOOC-\overset{\vert}{\underset{\vert}{C}}-H$
α-Cyano	$NC-\overset{\vert}{\underset{\vert}{C}}-COOH$	$NC-\overset{\vert}{\underset{\vert}{C}}-H$ or $HOOC-\overset{\vert}{\underset{\vert}{C}}-H$
α-Nitro	$O_2N-\overset{\vert}{\underset{\vert}{C}}-COOH$	$O_2N-\overset{\vert}{\underset{\vert}{C}}-H$
α-Aryl	$Ar-\overset{\vert}{\underset{\vert}{C}}-COOH$	$Ar-\overset{\vert}{\underset{\vert}{C}}-H$
α-Keto	$-\underset{\overset{\Vert}{O}}{C}-COOH$	$-\underset{\overset{\Vert}{O}}{C}-H$
α,α,α-Trihalo	$X_3C-COOH$	X_3CH
β-Keto	$-\underset{\overset{\Vert}{O}}{C}-\overset{\vert}{\underset{\vert}{C}}-COOH$	$-\underset{\overset{\Vert}{O}}{C}-\overset{\vert}{\underset{\vert}{C}}-H$
β,γ-Olefinic	$-\underset{\vert}{C}=\underset{\vert}{C}-\overset{\vert}{\underset{\vert}{C}}-COOH$	$-\underset{\vert}{C}=\underset{\vert}{C}-\overset{\vert}{\underset{\vert}{C}}-H$

It is likely that elimination occurs first, making this a special case of decarboxylation of α,β-olefinic acids. Glycidic acids give aldehydes on decarboxylation:



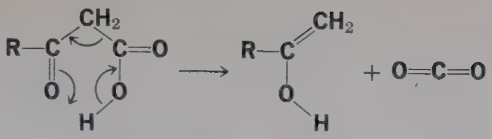
The direct product is an enol which tautomerizes to the aldehyde.[110] This is the usual last step in the Darzens reaction (reaction **6-43,** p. 700).

Decarboxylations may be regarded as reversals of the addition of carbanions to carbon dioxide (reaction **6-34,** p. 689), but free carbanions are not always involved.[111] When it is the carboxylate *ion* which is decarboxylated, the mechanism may be either S_E1 or S_E2. But some acids can also be decarboxylated directly, and in most of these cases there is a cyclic six-center mechanism:

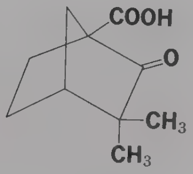
---

[110] Shiner and Martin, *J. Am. Chem. Soc.* **84**, 4824 (1962).

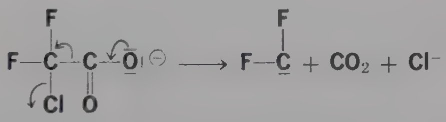
[111] For a review of the mechanism, see Brown, *Quart. Rev.* (*London*) **5**, 131–146 (1951).



Here too there is an enol which tautomerizes to the product. The mechanism is illustrated for the case of β-keto acids, but it is likely that malonic acids, α-cyano acids, α-nitro acids, and β,γ-unsaturated acids behave similarly, since similar six-membered transition states may be written for them. α,β-Olefinic acids are also decarboxylated by this mechanism, since they isomerize to the β,γ isomers before they actually decarboxylate.[112] Evidence for the cyclic mechanism is that β-keto acids which cannot, for steric reasons, form a six-membered ring (for example, **17**) resist decarboxylation.[113] Some acids which cannot form a six-membered transition state may still be decarboxylated directly, and these presumably react through an S_E2 mechanism. Although salts of α,α,α-trihalo acids decarboxylate via the S_E1 mechanism, as do most salts, the ClF_2CCOO^- ion is an exception. A carbene intermediate is involved in this case:[114]



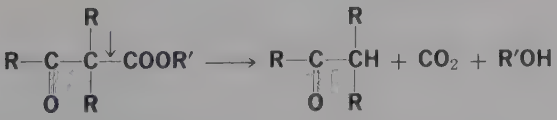
17



$$F{-}\overset{F}{\underset{Cl}{C}}{-}\underset{O}{\overset{}{\underset{\|}{C}}}{-}\underline{\overline{O}}|^{\ominus} \longrightarrow F{-}\overset{F}{\underset{}{\underline{C}}} + CO_2 + Cl^-$$

Since Cl^- is lost in the process, very little of the normal decarboxylation product (F_2ClCH) is found.

Although β-keto acids are easily decarboxylated, this reaction is seldom performed. The reason is that such acids are usually prepared from β-keto esters, and the esters are easily decarboxylated themselves, without isolation of the acids. This decarboxylation of β-keto esters involving cleavage on the



$$R{-}\underset{O}{\underset{\|}{C}}{-}\overset{R}{\underset{R}{C}}{\downarrow}COOR' \longrightarrow R{-}\underset{O}{\underset{\|}{C}}{-}\overset{R}{\underset{R}{C}}H + CO_2 + R'OH$$

---

[112] Bigley, *J. Chem. Soc.* **1964**, 3897.

[113] Wasserman, in Newman, "Steric Effects in Organic Chemistry," p. 352, John Wiley & Sons, Inc., New York, 1956.

[114] Hine and Duffey, *J. Am. Chem. Soc.* **81**, 1131 (1959).

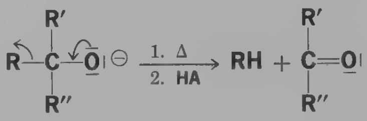
carboxyl side of the substituted methylene group (arrow) is carried out under acidic or neutral conditions to yield a ketone. When basic conditions are used, cleavage occurs on the other side of the CR_2 group (reaction **2-29**).

Some of the decarboxylations listed in *Organic Syntheses* are performed with concomitant ester or nitrile hydrolysis, and others are simple decarboxylations.

With ester or nitrile hydrolysis: OS **I,** 290, 451, 523; **II,** 200, 391; **III,** 281, 286, 317, 326, 510, 513, 591; **IV,** 55, 93, 176, 441, 664, 708, 790, 804; **44,** 59, 67, 86; **45,** 7, 25.

Simple decarboxylations: OS **I,** 351, 401, 440, 473, 475; **II,** 21, 61, 93, 229, 302, 333, 368, 416, 474, 512, 523; **III,** 213, 425, 495, 705, 733, 783; **IV,** 234, 254, 278, 337, 555, 560, 597, 630, 731, 857; **40,** 46; **46,** 28. Also see OS **IV,** 633.

2-27 Cleavage of alkoxides

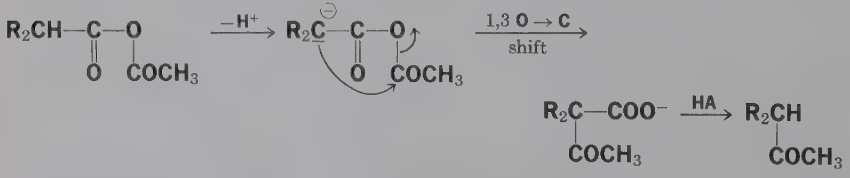


Alkoxides of tertiary alcohols may be cleaved, in a reaction which is essentially the reverse of addition of carbanions to ketones (reaction **6-31,** p. 684).[115] The reaction is unsuccessful when the R groups are simple unbranched alkyl groups, e.g., the alkoxide of triethylcarbinol. Cleavage is accomplished with branched alkoxides such as the alkoxides of triisopropylcarbinol or diisopropylneopentylcarbinol. The reaction also takes place when R is aryl; for example, the alkoxide of triphenylcarbinol gives benzene and benzophenone. The reaction has been used for extensive mechanistic studies (see p. 447).

2-28 Replacement of a carboxyl group by an acyl group

$$R_2CHCOOH + (CH_3CO)_2O \longrightarrow R_2CHCOCH_3 + CO_2 + CH_3COOH$$

When a carboxylic acid containing at least one α hydrogen is treated with an anhydride, it sometimes happens that decarboxylation occurs, accompanied by entrance of an acyl group. The reaction is aided by the presence of γ and δ NR_2 groups.[116] The first step is probably the formation of the mixed anhydride, $R_2CHCOOCOCH_3$, by an acid-anhydride exchange (see reaction **0-30,** p. 325). What happens next is not certain, but a 1,3-shift following loss of the α proton has been proposed:[117]



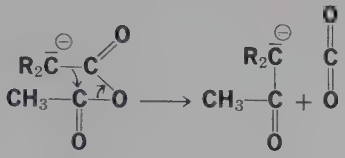
---

[115] Zook, March, and Smith, *J. Am. Chem. Soc.* **81**, 1617 (1959).

[116] Cruickshank and Sheehan, *J. Am. Chem. Soc.* **83**, 2891 (1961).

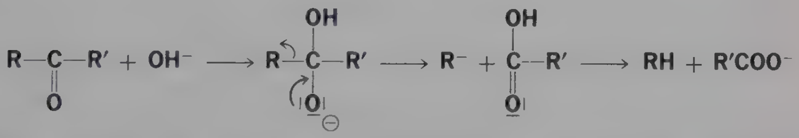
[117] Buchanan and McArole, *J. Chem. Soc.* **1952**, 2944; Smith and Fahey, *J. Am. Chem. Soc.* **81**, 3391 (1959).

The 1,3-shift and the decarboxylation may occur in one step:[118]



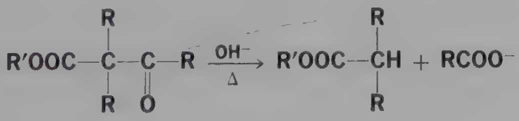
This reaction was an important step in the total synthesis of strychnine.[119]
OS **IV,** 5; **45,** 1.

B. Acyl cleavages. In these reactions (**2-29** to **2-32**) a carbonyl group is attacked by a hydroxide ion (or amide ion), giving an intermediate which undergoes cleavage to a carboxylic acid (or a carboxylic acid amide). With respect to the leaving group, this is nucleophilic substitution at a carbonyl group, and the mechanism is the tetrahedral one discussed in Chapter 10 (p. 274).

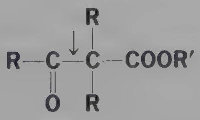


With respect to R, of course, this is electrophilic substitution. Indications are that the mechanism is usually S_E1.

2-29 Basic cleavage of β-keto esters and β-diketones



When β-keto esters are treated with base, cleavage occurs, but is on the keto side of the CR_2 group (arrow) in contrast to the acid cleavage mentioned on



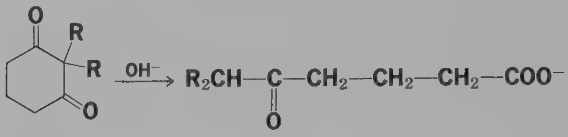
$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{\downarrow}\overset{\overset{R}{|}}{\underset{\underset{R}{|}}{C}}{-}COOR'}$

page 479. The products are an ester and the salt of an acid. However, the utility of the reaction is somewhat limited by the fact that decarboxylation is a side reaction, even under basic conditions. β-Diketones behave similarly to give a ketone and a carboxylic acid. The reaction has often been applied to cyclic β-diketones:[120]

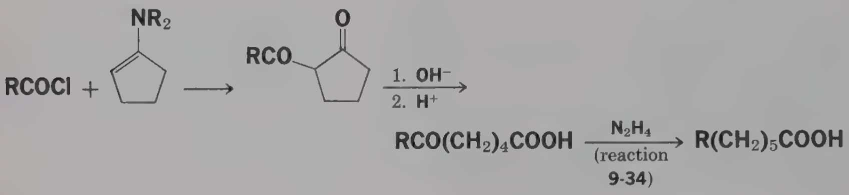
---

[118] Woodward, Cava, Ollis, Hunger, Daeniker, and Schenker, *Tetrahedron* **19**, 247 (1963).

[119] Ref. 118, p. 260 (XXXIX ⟶ XL in that paper).

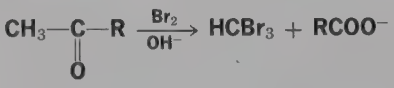


A combination of reaction **2-10** and this reaction has been used as a method of extending a chain by five or six carbons (illustrated for five):[121]



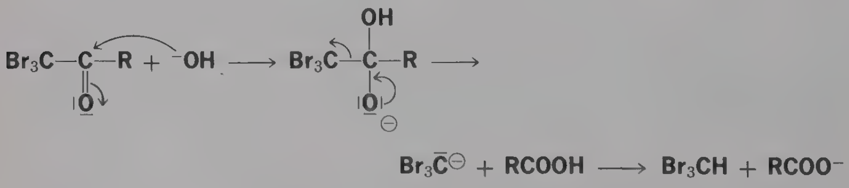
OS **II,** 266, 531; **III,** 379; **IV,** 415, 957; **43,** 34.

2-30 The haloform reaction



$$CH_3-\underset{\underset{O}{\|}}{C}-R \xrightarrow[OH^-]{Br_2} HCBr_3 + RCOO^-$$

In the *haloform reaction,* methyl ketones (and the only methyl aldehyde, acetaldehyde) are cleaved with halogen and a base. The halogen may be bromine, chlorine, or iodine. What takes place is actually a combination of two reactions. The first is an example of reaction **2-4,** in which, under the basic conditions employed, the methyl group is trihalogenated. Then the resulting trihalo ketone is attacked by hydroxide ion:



Primary or secondary methylcarbinols also give the reaction, since they are oxidized to the carbonyl compounds under the conditions employed. As with reaction **2-4,** the rate-determining step is the preliminary enolization of the methyl ketone.[122] A side reaction is α halogenation of the nonmethyl R group. Sometimes these groups are also cleaved.[123] The haloform reaction is often used as a test for methylcarbinols and methyl ketones. Iodine is most often used as the test reagent, since iodoform is an easily identifiable yellow solid.

---

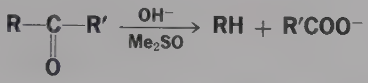
[120] For a review, see Stetter, in Foerst, "Newer Methods of Preparative Organic Chemistry," vol. 2, pp. 51–99, Academic Press Inc., New York [this article also appeared in *Angew. Chem.* **67,** 769 (1955)].

[121] Hünig and Lendle, *Chem. Ber.* **93,** 913 (1960); Hünig and Salzwedel, *Chem. Ber.* **99,** 823 (1966).

[122] Pocker, *Chem. Ind.* (*London*) **1959,** 1383.

OS **I,** 526; **II,** 428; **III,** 302; **IV,** 345; **42,** 4.

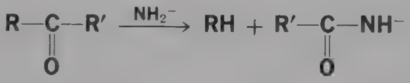
2-31 Cleavage of nonenolizable ketones



$$R-\underset{\underset{O}{\|}}{C}-R' \xrightarrow[Me_2SO]{OH^-} RH + R'COO^-$$

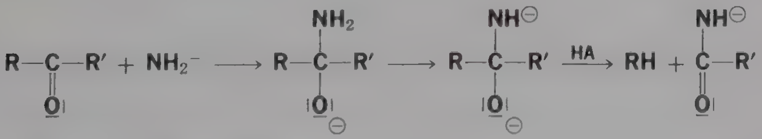
Ordinary ketones are much more difficult to cleave than are trihalo ketones or β-diketones, since the carbanion intermediates in these cases are more stable than simple carbanions. However, nonenolizable ketones may be cleaved in dimethyl sulfoxide at room temperature if a strong base (for example, *tert*-BuOK) is present.[124]

2-32 The Haller-Bauer reaction



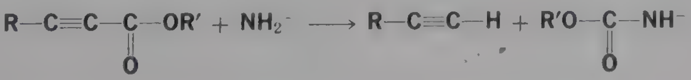
$$R-\underset{\underset{O}{\|}}{C}-R' \xrightarrow{NH_2^-} RH + R'-\underset{\underset{O}{\|}}{C}-NH^-$$

Cleavage of ketones with sodium amides is called the *Haller-Bauer reaction.*[125] As with reaction **2-31,** which is exactly analogous, the reaction is usually applied only to nonenolizable ketones. It is most often applied to ketones of the form $ArCOCR_3$, where the products, R_3CCONH_2, are not easily attainable by other methods. However, many other ketones have been used, though benzophenone is virtually unaffected. It has been shown that the configuration of optically active R is retained.[126] The NH_2 loses its proton *before* the R is cleaved:[127]



$$R-\underset{\underset{\overline{O}|}{\|}}{C}-R' + NH_2^- \longrightarrow R-\overset{\overset{NH_2}{|}}{\underset{\underset{|\overline{O}|^{\ominus}}{|}}{C}}-R' \longrightarrow R-\overset{\overset{NH^{\ominus}}{|}}{\underset{\underset{|\overline{O}|^{\ominus}}{|}}{C}}-R' \xrightarrow{HA} RH + \overset{\overset{NH^{\ominus}}{|}}{\underset{\underset{\overline{O}|}{\|}}{C}}-R'$$

A very similar reaction may be applied to esters and amides of α,β-acetylenic acids with no γ hydrogen:[128]



$$R-C\equiv C-\underset{\underset{O}{\|}}{C}-OR' + NH_2^- \longrightarrow R-C\equiv C-H + R'O-\underset{\underset{O}{\|}}{C}-NH^-$$

Carbamates are obtained from esters, and ureas from amides.

OS **40,** 103; **42,** 41.

---

[123] Levine and Stephens, *J. Am. Chem. Soc.* **72,** 1642 (1950).

[124] Gassman and Zalar, *Tetrahedron Letters* **1964,** 3031.

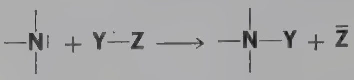
[125] For a review, see Hamlin and Weston, *Org. Reactions* **9,** 1-36 (1957).

[126] Impastato and Walborsky, *J. Am. Chem. Soc.* **84,** 4838 (1962).

[127] Bunnett and Hrutfiord, *J. Org. Chem.* **27,** 4152 (1962).

[128] Craig and Moyle, *J. Chem. Soc.* **1963,** 4402.

Electrophilic Substitution at Nitrogen. In each of the reactions in this section, an electrophile bonds with the unshared pair of a nitrogen. The electrophile may be a free positive ion or may be a positive species attached to a carrier which breaks off in the course of the attack or shortly after:



$$-\overset{|}{\underset{|}{N}}| + Y-Z \longrightarrow -\overset{|}{\underset{|}{N}}-Y + \bar{Z}$$

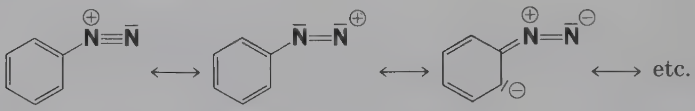
18

Further reaction of **18** depends on the nature of Y and of the other groups attached to the nitrogen.

2-33 Diazotization

$$Ar-NH_2 + HONO \longrightarrow Ar-\overset{\oplus}{N}\equiv\bar{N}$$

When primary aromatic amines are treated with nitrous acid, diazonium salts are formed.[129] The reaction also occurs with aliphatic primary amines, but these are extremely unstable, even in solution (see p. 291). Aromatic diazonium ions are more stable, because of resonance interaction between the nitrogens and the ring:



19 **20**

Incidentally, **19** contributes more to the hybrid than **20**, as shown by bond-distance measurements. In benzenediazonium chloride, the C—N distance is 1.42 Å, and the N—N distance 1.11 Å,[130] which values fit more closely to a single and a triple bond than to two double bonds (see p. 22). Even aromatic diazonium salts are stable only at low temperatures, usually only below 5°, though more stable ones, such as the diazonium salt obtained from sulfanilic acid, are stable up to 10 or 15°. It is possible to prepare solid diazonium salts if desired.[131]

For aromatic amines, the reaction is very general. Halogen, nitro, alkyl, aldehyde, sulfonic acid, etc., groups do not interfere. Since aliphatic amines do not react with nitrous acid below a pH of about 3, it is even possible, by working at a pH of about 1, to diazotize an aromatic amine *without disturbing* an aliphatic amino group in the same molecule.[132]

If an aliphatic amino group is α to a COOR, CN, CHO, COR, etc., and has an α hydrogen, then treatment with nitrous acid gives not a diazonium salt, but a *diazo compound:*

---

[129] For reviews, see Ridd, *Quart. Rev.* (*London*) **15,** 418–441 (1961); Belov and Kozlov, *Russ. Chem. Rev.* **32,** 59–75 (1963), pp. 59–65; Zollinger, "Azo and Diazo Chemistry," pp. 1–37, Interscience Publishers, Inc., New York, 1961.

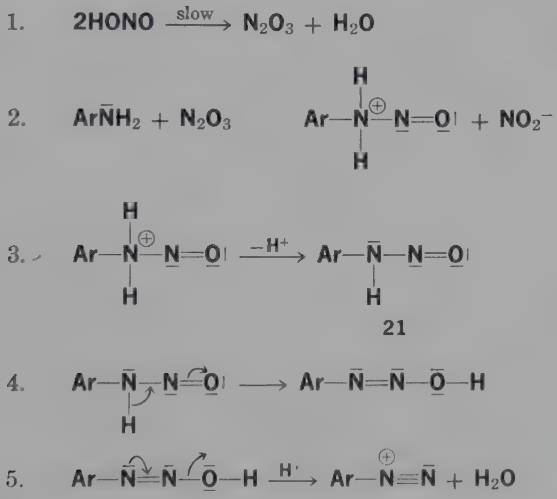
[130] Rømming, *Acta Chem. Scand.* **13,** 1260 (1959).

[131] For example, see Hodgson and Mahadevan, *J. Chem. Soc.* **1947,** 325; Piercey and Ward, *J. Chem. Soc.* **1962,** 3841.

[132] Kornblum and Iffland, *J. Am. Chem. Soc.* **71,** 2137 (1949).

$$\mathrm{EtOOC{-}CH_2{-}NH_2 + HONO \longrightarrow EtOOC{-}CH{=}\overset{\oplus}{N}{=}\overset{\ominus}{\underline{\bar{N}}}}$$

Despite the fact that diazotization takes place in acid solution, the actual species which is attacked is not the salt of the amine, except at high acidities, but the small amount of free amine present.[133] It is because aliphatic amines are stronger bases than aromatic ones, that at pH's below 3, there is not enough free amine present for the former to be diazotized, while the latter still undergo the reaction. In dilute acid the actual attacking species is N_2O_3, which acts as a carrier of NO^+. Evidence for this is that the reaction is second order in nitrous acid, and at sufficiently low acidities, the amine does not appear in the rate expression.[134] Under these conditions the mechanism is



21

There exists other evidence for this mechanism.[135] Other attacking species may be NOCl, $H_2NO_2^+$, and, at high acidities, even NO^+ itself.

There are many preparations of diazonium salts listed in *Organic Syntheses,* but they are always prepared for use in other reactions. We do not list them here, but under reactions in which they are used. The preparation of aliphatic diazo compounds may be found at OS **III,** 392; **IV,** 424.

2-34 The conversion of hydrazines to azides

$$\mathrm{RNHNH_2 + HONO \longrightarrow R{-}\bar{N}{=}\overset{(+)}{N}{=}\overset{(\ )}{\underline{\bar{N}}}}$$

---

[133] Challis and Ridd, *J. Chem. Soc.* **1962,** 5197, 5208; Challis, Larkworthy, and Ridd, *J. Chem. Soc.* **1962,** 5203.

[134] Hughes, Ingold, and Ridd, *J. Chem. Soc.* **1958,** 58, 65, 77, 88; Hughes and Ridd, *J. Chem. Soc.* **1958,** 70, 82.

[135] For a discussion, see Ridd, Ref. 129, pp. 422–424.

Monosubstituted hydrazines, treated with nitrous acid, give azides, in a reaction which is exactly analogous to the formation of aliphatic diazo compounds mentioned in reaction **2-33.**

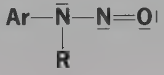
OS **III,** 710; **IV,** 819; **44,** 15.

2-35 N-Nitrosation

$$R_2NH + HONO \longrightarrow R_2N{-}NO$$

When secondary amines are treated with nitrous acid, N-nitroso compounds are formed.[136] The reaction may be accomplished with dialkyl-, diaryl-, or alkylarylamines, and even with mono-N-substituted amides: $RCONHR' + HONO \longrightarrow RCON(NO)R'$. Tertiary amines have also been N-nitrosated, but in these cases, one group cleaves, so that the product is the nitroso derivative of a secondary amine.[137] The group which cleaves appears as an aldehyde or ketone.

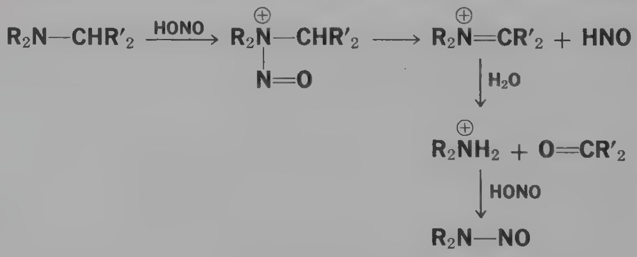
The mechanism of nitrosation is essentially the same as in reaction **2-33** up to the point where **22** (analogous to **21**) is formed. Since this species



$$Ar{-}\overline{N}{-}\underline{N}{=}\underline{O}| \quad (\text{R on } N)$$

22

cannot lose a proton, it is stable and the reaction ends there. The attacking entity may be any of those mentioned in reaction **2-33.** The following has been suggested as the mechanism for the reaction with tertiary amines:[138]



The evidence for this mechanism includes the facts that nitrous oxide is a product (formed by $2HNO \longrightarrow H_2O + N_2O$) and that quinuclidine, where the nitrogen is at a bridgehead and therefore cannot give elimination, did not react.[138]

Amines and amides may be N-*nitrated* with N_2O_5[139] and converted to triazenes with diazonium salts. C-Nitrosation is discussed at reactions **1-3** (p. 398) and **2-7** (p. 462).

---

[136] For reviews, see Ridd, Ref. 129; and Turney and Wright, *Chem. Rev.* **59,** 497–513 (1959), pp. 498–504.

[137] Hein, *J. Chem. Educ.* **40,** 181 (1963).

[138] Smith and Loeppky, *J. Am. Chem. Soc.* **89,** 1147 (1967); Smith and Pars, *J. Org. Chem.* **24,** 1324 (1959).

[139] Emmons, Pagano, and Stevens, *J. Org. Chem.* **23,** 311 (1958); Runge and Treibs, *J. prakt. Chem.* [4] **15,** 223 (1962); Halevi, Ron, and Speiser, *J. Chem. Soc.* **1965,** 2560.

OS **I,** 177, 399, 417; **II,** 163, 211, 290, 460, 461, 462, 464 [also see **43,** 86]; **III,** 106, 244; **IV,** 718, 780, 943; **42,** 69; **43,** 83; **45,** 96. Also see OS **III,** 711.

2-36 N-Halogenation

$$\mathrm{RNH_2 + NaOCl \longrightarrow RNHCl}$$

Treatment with sodium hypochlorite or hypobromite converts primary amines into N-halo- or N,N-dihaloamines. Secondary amines may be converted to N-halo secondary amines. Similar reactions may be carried out on unsubstituted and N-substituted amides and on sulfonamides. With unsubstituted amides the N-halogen product is seldom isolated, but usually rearranges (see reaction **8-15,** p. 816); however, N-halo-N-alkyl amides and N-halo imides are quite stable. The important reagent N-bromosuccinimide is made in this manner. N-Halogenation has also been accomplished with other reagents, for example, *tert*-BuOCl.[140] The mechanism involves an attack by a positive halogen and is probably similar to that of reactions **2-33** and **2-35.**

OS **III,** 159; **IV,** 104, 157; **41,** 82; **42,** 73; **45,** 16.

---

[140] Altenkirk and Israelstam, *J. Org. Chem.* **27,** 4532 (1962).

CHAPTER THIRTEEN

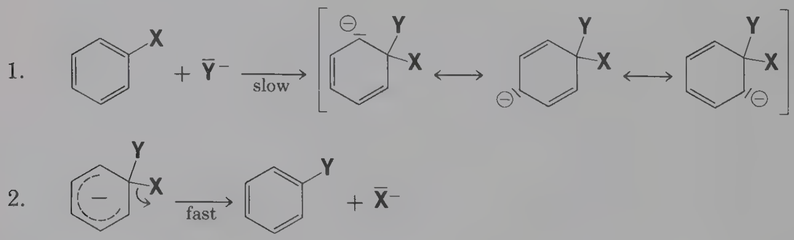
Aromatic Nucleophilic Substitution

On page 282 it was pointed out that nucleophilic substitutions proceed so slowly at an aromatic carbon that the reactions of Chapter 10 are not feasible for aromatic substrates. There are, however, exceptions to this statement, and it is these exceptions which form the subject of this chapter.[1] Reactions which *are* successful at an aromatic substrate are largely of three kinds: (1) reactions activated by electron-withdrawing groups ortho and para to the leaving group; (2) reactions catalyzed by very strong bases, proceeding through aryne intermediates (see p. 492); and (3) reactions in which the nitrogen of a diazonium salt is replaced by a nucleophile. However, not all of the reactions discussed in this chapter fit into these categories.

MECHANISMS

Each of the three principal mechanisms is similar to one of the aliphatic nucleophilic substitution mechanisms discussed in Chapter 10.[2]

The Intermediate-complex Mechanism. By far the most important mechanism for nucleophilic aromatic substitution consists of two steps:



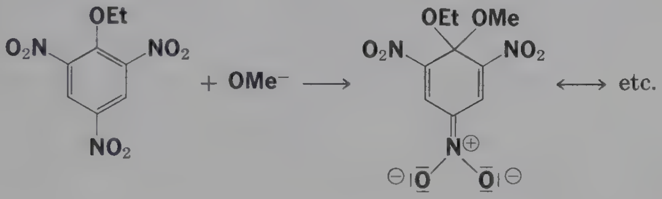
The first step is usually, but not always, rate-determining. It may be seen that this mechanism greatly resembles the tetrahedral mechanism discussed in Chapter 10 (p. 274) and, in another way, the σ-complex mechanism of electrophilic aromatic substitution (p. 376). In all three cases, the attacking species forms a bond with the substrate, giving an intermediate, and then the leaving group departs. This mechanism is sometimes called the S_N2 mechanism, because it is bimolecular, but in this book we reserve that name for nucleophilic substitutions in which attack and departure are simultaneous, so that there is no intermediate. We shall refer to this mechanism as the *intermediate-complex mechanism,* emphasizing its similarity to the σ-complex mechanism of electrophilic substitution.

---

[1] For a review of aromatic nucleophilic substitution, see Bunnett and Zahler, *Chem. Rev.* **49**, 273–412 (1951).

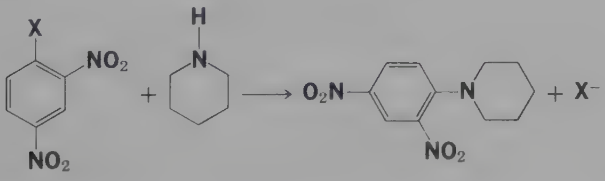
[2] For reviews of aromatic nucleophilic substitution mechanisms, see Ref. 1; Bunnett, *Quart. Rev.* (*London*) **12**, 1–16 (1958); Sauer and Huisgen, *Angew. Chem.* **72**, 294–315 (1960); and Ross, *Progr. Phys. Org. Chem.* **1**, 31–74 (1963).

There is a great deal of evidence for the mechanism, and we shall discuss only some of it.[3] Probably the most convincing evidence was the isolation, as long ago as 1902, of the intermediate **1,** in the reaction between ethyl picrate and methoxide ion.[4] Intermediates of this type are stable salts,



1

called *Meisenheimer salts,* and many more of them have been isolated since 1902. The structures of two of these intermediates (one with two methoxy groups at the 1-position, and one with a methoxy and a hydrogen) have been proved by nuclear magnetic resonance.[5] Further evidence comes from studies of the effect of the leaving group on the reaction. If the mechanism were similar to either the S_N1 or S_N2 mechanisms described in Chapter 10, then the Ar—X bond would be broken in the rate-determining step. In the intermediate-complex mechanism this bond is not broken until after the rate-determining step (that is, if step 1 is rate-determining). We would predict from this that, if the intermediate-complex mechanism is operating, a change in leaving group should not have much effect on the rate of the reaction. In the reaction



when X was Cl, Br, I, SOPh, SO_2Ph, or *p*-nitrophenoxy, the rates differed only by a factor of about 5.[6] This behavior would not be expected in a reaction in which the Ar—X bond is broken in the rate-determining step. We do not expect the rates to be *identical,* because the nature of X affects the rate at which Y attacks. An increase in the electronegativity of X causes a decrease in the electron density around the substrate carbon, resulting in a faster attack by a nucleophile. Thus, in the reaction just mentioned, when X = F, the relative rate was 3300 (compared to I = 1). The very fact that fluoro is the best leaving group among the halogens in most aromatic nucleophilic substitutions is good evidence that the mechanism is different from the S_N1 and the S_N2 mechanisms, where fluoro is by far the poorest leaving group of the halogens.

---

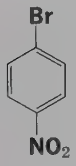
[3] Ross, Ref. 2, pp. 38–66, gives a lengthy summary of the evidence.

[4] Meisenheimer, *Ann.* **323,** 205 (1902).

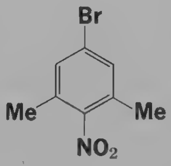
[5] Crampton and Gold, *J. Chem. Soc.* **1964,** 4293. Also see Foster, Fyfe, and Morris, *Rec. trav. chim.* **84,** 516 (1965); Foster and Fyfe, *Tetrahedron* **21,** 3372 (1965); and Servis, *J. Am. Chem. Soc.* **87,** 5497 (1965).

[6] Bunnett, Garbisch, and Pruitt, *J. Am. Chem. Soc.* **79,** 385 (1957).

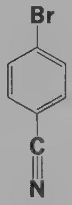
Other evidence focuses on the intermediate. If the intermediate-complex mechanism is correct, then the reason that electron-withdrawing groups accelerate the reaction is that they spread the negative charge of the intermediate, through resonance (see **1**). In that case, anything which decreases the resonance interaction between the activating group and the ring should decrease the rate. In accord with this, **2** reacts with piperidine 27 times faster than **3**. However, in going from **4** to **5**, the rate is decreased only by a factor of 4, since the linear CN group is pushed out of planarity to a smaller extent than is the nitro group.[7]



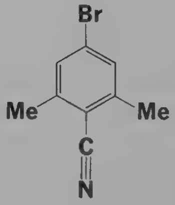
2



3

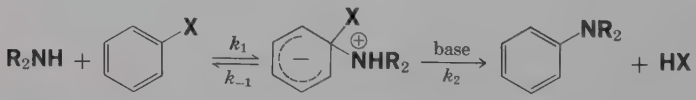


4



5

The pattern of base catalysis of reactions with amine nucleophiles provides additional evidence. These reactions are catalyzed by bases only when a relatively poor leaving group (such as OR) is present (not Cl or Br) and only when relatively bulky amines are nucleophiles.[8] Bases could not catalyze step 1, but if amines are nucleophiles, bases can catalyze step 2, by removing a proton from the intermediate.



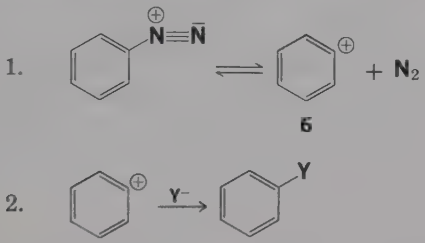
Base catalysis is found precisely in those cases where the amine moiety cleaves easily but X does not, so that k_{-1} is large and step 2 is rate-determining. This is evidence for the intermediate-complex mechanism because it implies two steps. Furthermore, in cases where bases *are* catalysts, they catalyze only at low base concentrations:[8] a plot of the rate against the base concentration shows that small increments of base rapidly increase the rate, until a certain concentration of base is reached, after which further base

[7] Spitzer and Wheland, *J. Am. Chem. Soc.* **62,** 2995 (1940).

[8] Kirby and Jencks, *J. Am. Chem. Soc.* **87,** 3217 (1965); Bunnett and Garst, *J. Am. Chem. Soc.* **87,** 3875, 3879 (1965); Bunnett and Berasconi, *J. Am. Chem. Soc.* **87,** 5209 (1965).

addition no longer greatly affects the rate. This behavior, based on a partitioning effect (see p. 378), is also evidence for the intermediate-complex mechanism. At low base concentration, each increment of base, by increasing the rate of step 2, increases the fraction of intermediate which goes to product rather than reverting to reactants. At high base concentration the process is virtually complete: there is very little reversion to reactants, and the rate becomes dependent on step 1. Just how bases catalyze step 2 is not certain.[9]

The S_N1 Mechanism. For aryl halides, even active ones, a unimolecular S_N1 mechanism has never been observed with certainty. It is with diazonium salts that this mechanism is important:[10]



Evidence for the S_N1 mechanism[11] is as follows:

1. The reaction rate is first order in diazonium salt and independent of the concentration of Y.
2. When high concentrations of halide salts are added, the product is an aryl halide, but the rate is independent of the concentration of the added salts.
3. The effects of ring substituents on the rate are consistent with a unimolecular rate-determining cleavage.[12]
4. That the first step is a reversible cleavage was demonstrated by the observation that when $Ar^{15}\overset{\oplus}{N}\equiv N$ was the reacting species, recovered starting material contained not only $Ar^{15}\overset{\oplus}{N}\equiv N$, but also $Ar\overset{\oplus}{N}\equiv {}^{15}N$.[13] This could arise only if the nitrogen breaks away from the ring and then returns. However, there is evidence that the nitrogen does not *completely* break away and that there are at least two intermediates in which the nitrogen is somehow bonded to the ring, one of them being perhaps the charged cage pair $Ar^+ \quad N_2$.

It is likely that the aryl cations formed in these reactions do not have the simple structure represented as **6**. The fact that electron-spin-resonance spectra are obtained from these solutions indicates that the carbonium ion has unpaired electrons.[14] The simplest way to explain this is to assume that the ion has a diradical structure

---

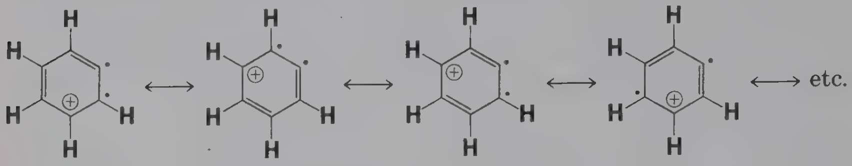
[9] For example, see Pietra, *Tetrahedron Letters* **1965**, 2405.

[10] Aryl iodonium salts, Ar_2I^+, also undergo substitutions by this mechanism (and by a free-radical mechanism).

[11] The evidence is summarized in Zollinger, "Azo and Diazo Chemistry," pp. 138–142, Interscience Publishers, Inc., New York, 1961.

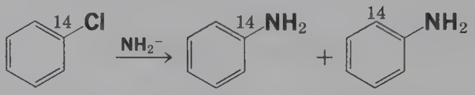
[12] Lewis and Miller, *J. Am. Chem. Soc.* **75**, 429 (1953).

[13] Lewis and Insole, *J. Am. Chem. Soc.* **86**, 32 (1964).



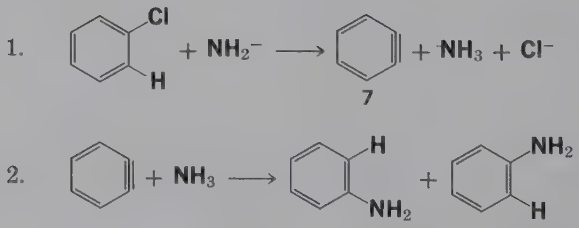
or that the diradical is in equilibrium with **6**.[15]

The Benzyne Mechanism.[16] Some aromatic nucleophilic substitutions are clearly different in character from those which occur by the intermediate-complex mechanism (or the S_N1 mechanism). These substitutions occur on aryl halides which have no activating groups; bases are required which are stronger than those normally used; and, most interesting of all, the incoming group does not always take the position vacated by the leaving group. That the latter statement is true was elegantly demonstrated by the reaction of 1-^{14}C-chlorobenzene with potassium amide:



The product consisted of aniline, half of which was labeled in the 1-position and half in the 2-position.[17]

A mechanism which can explain all these observations involves elimination followed by addition:



The symmetrical intermediate **7** can be attacked by the nitrogen at either of two positions, explaining why half of the aniline produced from the radioactive chlorobenzene was labeled at the 2-position. Other evidence for this mechanism is the following:

---

[14] Abramovitch, Hymers, Rajan, and Wilson, *Tetrahedron Letters* **1963**, 1507. See also Abramovitch and Saha, *Can. J. Chem.* **43**, 3269 (1965).

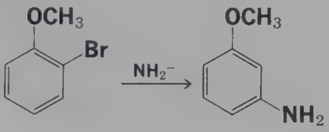
[15] The idea that aryl carbonium ions might be diradicals was first suggested by Taft, *J. Am. Chem. Soc.* **83**, 3350 (1961).

[16] For reviews, see Heaney, *Chem. Rev.* **62**, 81–97 (1962); Bunnett, *J. Chem. Educ.* **38**, 278–285 (1961); Huisgen and Sauer, *Angew. Chem.* **72**, 91–108 (1960); Jenny, Caserio, and Roberts, *Experientia* **14**, 348 (1958); Wittig, *Pure Appl. Chem.* **7**, 173–191 (1963), *Angew. Chem. Intern. Ed. Engl.* **4**, 731–737 (1965).

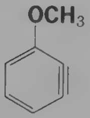
[17] Roberts, Semenow, Simmons, and Carlsmith, *J. Am. Chem. Soc.* **78**, 601 (1956).

1. If the aryl halide contains two ortho substituents, the reaction should not be able to occur. This is indeed the case.[17]

2. It had been known for many years before this mechanism was suggested, that aromatic nucleophilic substitution occasionally results in substitution at a different position. This is called *cine substitution* and may be illustrated by the following reaction:[18]



In this particular case, only the meta isomer is formed. The reason that a 1:1 mixture is not formed is that the intermediate (**8**) is not symmetrical and



8

the methoxy group directs the incoming group meta but not ortho (see p. 497).

3. The fact that the order of halide reactivity is $Br > I > Cl \gg F$ (when the reaction is performed with KNH_2 in liquid NH_3) shows that the ordinary intermediate-complex mechanism is not operating here.[17]

A study of the effect of the leaving group has been used to examine the mechanism of the first step of the reaction, to determine whether the hydrogen or the halogen is lost first. The available evidence points to the conclusion that the hydrogen departs first, and then the halide ion.[19]

Species such as **7** and **8** are called *benzynes* or, more generally, *arynes,* and the mechanism is known as the *benzyne mechanism.* Benzynes differ from the species discussed in Chapter 5 in that each carbon has a valence of four. However, they are very reactive, as are the species in that chapter. No aryne has yet been isolated, though spectra of transient benzynes have been detected,[20] and benzynes may be trapped (for example, they undergo the Diels-Alder reaction; see reaction **5-34,** p. 626). That they are highly reactive is indicated not only by the failure to isolate them, but also by their low selectivity. When bromobenzene is treated with amide ion in the presence of other nucleophiles, a considerable lack of selectivity is noted.[21] This reactivity is undoubtedly caused by the strain in a six-membered ring containing a triple bond. It should be noted that the extra pair of electrons does not affect the aromaticity. The original sextet still functions as a closed ring, and the two additional electrons are merely located in a π orbital which covers only two carbons. Not only benzene rings, but other aromatic rings[22] and even nonaromatic rings (see p. 280) can react through triple-bond-containing intermediates.

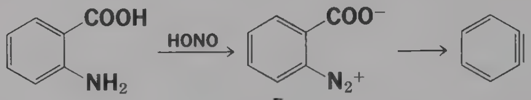
---

[18] This example is from Gilman and Avakian, *J. Am. Chem. Soc.* **67,** 349 (1945). For a table of many such examples, see Ref. 1, pp. 385–386.

[19] Huisgen, in "Theoretical Organic Chemistry, The Kekulé Symposium," p. 158, Butterworth Scientific Publications, London, 1959; Roberts, Vaughan, Carlsmith, and Semenow, *J. Am. Chem. Soc.* **78,** 611 (1956); Bunnett, Ref. 2, p. 7.

[20] Berry, Spokes, and Stiles, *J. Am. Chem. Soc.* **84,** 3570 (1962). Benzynes have also been detected by mass spectroscopy. Fisher and Lossing, *J. Am. Chem. Soc.* **85,** 1018 (1963); Berry, Clardy, and Schafer, *J. Am. Chem. Soc.* **86,** 2738 (1964).

There are other ways to prepare benzyne intermediates.[23] Probably the most convenient method involves thermal or photolytic decomposition of the product of diazotization of anthranilic acid or its derivatives:[24]



9

The zwitterion (**9**) decomposes to give the highly reactive benzyne.

Other Mechanisms. There is no clear-cut proof that a one-step S_N2 mechanism, so important at a saturated carbon, ever actually occurs with an aromatic substrate. However, a number of facts are in agreement with the possibility, in certain cases,[25] especially in those cases where fluoro is a poor leaving group, since this would be consistent with an S_N2 process, but not with the intermediate-complex mechanism as shown on page 488. On the other hand, an intermediate-complex mechanism in which the *second* step was rate-determining would be quite compatible with reactions in which fluoro is a poor leaving group, and some of them have been shown to operate by such a process.[26] The aromatic S_N2 process is sometimes called the "one-stage" mechanism to distinguish it from the "two-stage" intermediate-complex mechanism.

Some of the reactions in this chapter operate by still other mechanisms, among them an addition-elimination mechanism (see reaction **3-17**).

REACTIVITY

The Effect of Substrate Structure. In the discussion of electrophilic aromatic substitution (Chapter 11) equal attention was paid to the effect of substrate structure on reactivity (activation or deactivation) and on orientation. The question of orientation was important because in a typical substitution there are four or five hydrogens which could serve as leaving groups. This type of question is much less important for aromatic nucleophilic substitution, since in most cases there is only one potential leaving group in a molecule. Therefore attention is largely focused on the reactivity of one molecule as compared with another and not on the comparison of the reactivity of different positions within the same molecule. However, there *have* been studies of the latter question.[27] For example, the nitro group has been shown to be ortho-para-directing, by the observation that pentafluoronitrobenzene gave 95% of a mixture of 2-nitro-3,4,5,6-tetrafluoroaniline and 4-nitro-2,3,5,6-tetrafluoroaniline, when treated with ammonia:[28]

---

[21] Scardiglia and Roberts, *Tetrahedron* **3**, 197 (1958).

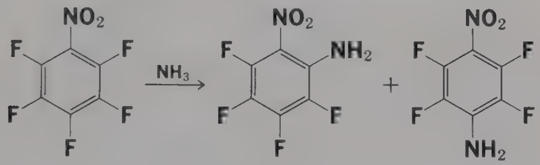
[22] For a review of *hetarynes* (benzyne intermediates in heterocyclic rings), see Kauffman, *Angew. Chem. Intern. Ed. Engl.* **4**, 543–557 (1965).

[23] For example, see Wittig and Hoffmann, *Chem. Ber.* **95**, 2718, 2729 (1962); Köbrich, *Chem. Ber.* **96**, 2544 (1963); Günther, *Chem. Ber.* **96**, 1801 (1963); Wittig and Ebel, *Ann.* **650**, 20 (1961); Fields and Meyerson, *Chem. Commun.* **1965**, 474.

[24] Stiles and Miller, *J. Am. Chem. Soc.* **82**, 3802 (1962); Stiles, Miller, and Burckhardt, *J. Am. Chem. Soc.* **85**, 1792 (1963); Friedman and Logullo, *J. Am. Chem. Soc.* **85**, 1549 (1963).

[25] Chapman and Russell-Hill, *J. Chem. Soc.* **1956**, 1563; Parker and Read, *J. Chem. Soc.* **1962**, 9, 3149.

[26] Bunnett and Randall, *J. Am. Chem. Soc.* **80**, 6020 (1958).



Similarly, it was shown (for C_6F_5X) that the groups H, Me, CF_3, Cl, Br, I, SMe, and NMe_2 direct mostly to the para position, and NH_2 and O^- are largely meta-directing.[29]

Aromatic nucleophilic substitutions proceeding by the intermediate-complex mechanism are accelerated by electron-withdrawing groups, especially in positions ortho and para to the leaving group, and are hindered by electron-attracting groups. This is, of course, opposite to the effects of these groups on electrophilic substitutions, and the reasons are similar to those discussed in Chapter 11 (p. 382). Table 1 contains a list of groups arranged approximately in order of activating or deactivating ability. Hetero nitrogen atoms are also strongly activating (especially to the α and γ positions) and are even more so when quaternized. The N_2^+ group is seldom deliberately used to activate a reaction, but it sometimes happens that in the diazotization of a compound such as *p*-nitroaniline or *p*-chloroaniline, the group para to the diazonium group is replaced by OH from the solvent or by X from $ArN_2^+ \quad X^-$, to the surprise and chagrin of the investigator, who was trying only to replace the diazonium group, and to leave the para group untouched. By far the most common activating group is the nitro group.

Steric effects of ortho groups are usually not important, since the electrophile attacks perpendicular to the ring, but with large enough groups they may become important.

In reactions involving aryne intermediates, there are two factors which affect the position of the incoming group, the first being the direction in

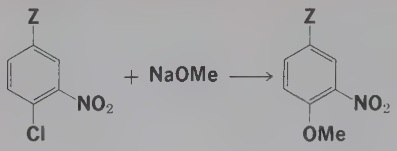
---

[27] See Burdon, Hollyhead, and Tatlow, *J. Chem. Soc.* **1965,** 6336; Burdon and Hollyhead, *J. Chem. Soc.* **1965,** 6326; and earlier papers in this series.

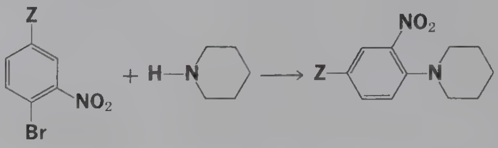
[28] Brooke, Burdon, and Tatlow, *J. Chem. Soc.* **1961,** 802; Allen, Burdon, and Tatlow, *J. Chem. Soc.* **1965,** 1045.

[29] Burdon, *Tetrahedron* **21,** 3373 (1965); Burdon, Coe, Marsh, and Tatlow, *Tetrahedron* **22,** 1183 (1966).

TABLE 1. Groups listed in approximate descending order of activating ability Reaction *a* is



at 0°.[30] Reaction *b* is

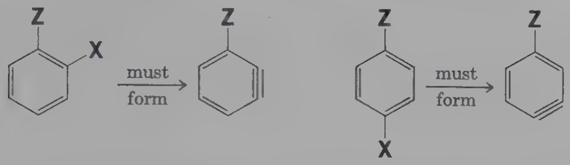


at 25°.[31] For reaction *a* the rates are relative to H, but for reaction *b* they are relative to NH_2

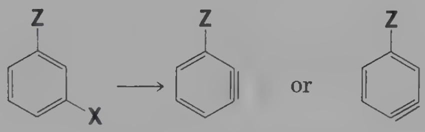
	Group Z	*Relative rate of reaction a* (H = 1)[30]	*Relative rate of reaction b* (NH_2 = 1)[31]
Activates halide exchange at room temperature	N_2^+		
Activates reaction with strong nucleophiles at room temperature	$\overset{+}{N}$—R (heterocyclic)		
Activate reactions with strong nucleophiles at 80–100°	NO	5.22 × 10^6	
	NO_2	6.73 × 10^5	very fast
	N (heterocyclic)		
With nitro also present, activate reactions with strong nucleophiles at room temperature	SO_2Me		
	NMe_3^+		
	CF_3		
With nitro also present, activate reactions with strong nucleophiles at 40–60°	CN	3.81 × 10^4	
	CHO	2.02 × 10^4	
	COR		
	COOH		
	SO_3^-		
	Br		6.31 × 10^4
	Cl		4.50 × 10^4
	I		4.36 × 10^4
	COO^-		2.02 × 10^4
	H	1	8.06 × 10^3
	F		2.10 × 10^3
	CMe_3		1.37 × 10^3
	Me		1.17 × 10^3
	OMe		145
	NMe_2		9.77
	OH		4.70
	NH_2		1

The comments on the left are from Ref. 1, p. 308.

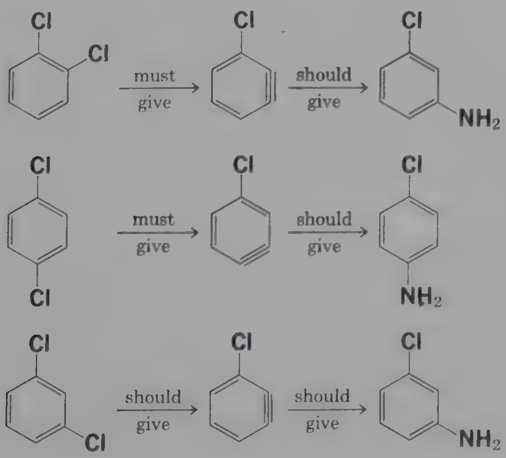
which the benzyne forms.[32] When there are groups ortho or para to the leaving group, there is no choice:



but when a meta group is present, the benzyne may form in two different ways:



In such cases, the more acidic hydrogen is removed. Since acidity is related to the inductive effect of Z, it may be stated that an electron-attracting Z favors removal of the ortho hydrogen, while an electron-donating Z favors removal of the para hydrogen. The second factor is that the benzyne, once formed, may be attacked at two positions. The favored position for nucleophilic attack is the one which leads to the more stable carbanion intermediate, and this in turn is also dependent on the inductive effect of Z. For $-I$ groups, the more stable carbanion is the one in which the negative charge is closer to the substituent. These principles are illustrated by the reaction of the three dichlorobenzenes with alkali-metal amides. The predicted products are



---

[30] Miller and Parker, *Australian J. Chem.* **11**, 302 (1958).

[31] Berliner and Monack, *J. Am. Chem. Soc.* **74**, 1574 (1952).

[32] This analysis is from Roberts, Vaughan, Carlsmith, and Semenow, *J. Am. Chem. Soc.* **78**, 611 (1956).

In each case the predicted product was the one chiefly formed,[33] though the para isomer also gave 19% *meta*-chloroaniline.[34] The obtention of *meta*-methoxyaniline, mentioned on page 493, is also in accord with these predictions.

Just as electrophilic aromatic substitutions were found more or less to follow the Hammett relationship (with σ^+ instead of σ; see p. 393), so do nucleophilic substitutions follow it, with σ^- instead of σ for electron-withdrawing groups.[35]

As was pointed out on page 391, the position of attack at alternant hydrocarbons is the same for electrophiles, nucleophiles, and free radicals.

The Effect of the Leaving Group. The common leaving groups in aliphatic nucleophilic substitution—halide, sulfate, sulfonate, NR_3^+, etc.—are also common leaving groups in aromatic nucleophilic substitutions, but the groups NO_2, OR, OAr, SO_2R, and SR, which are not lost in aliphatic systems, *are* leaving groups when attached to aromatic rings. Surprisingly, NO_2 is a particularly good leaving group. An approximate order of leaving-group ability is[36] $F > NO_2 > OTs > SOPh > Cl, Br, I > N_3 > NR_3^+ > OAr, OR, SR, SO_2R, NH_2$. However, this is greatly dependent on the nature of the nucleophile, as is illustrated by the fact that $C_6Cl_5OCH_3$ treated with NH_2^- gives mostly $C_6Cl_5NH_2$; that is, one methoxy group is replaced in preference to five chlorines.[37] As usual, OH can be a leaving group if it is converted to an inorganic ester. Among the halogens, fluoro is generally a much better leaving group than the other halogens, which have reactivities fairly close together. The order is usually $Cl > Br > I$, but not always.[38] The leaving-group order is quite different from that for the S_N1 or S_N2 mechanisms. The most likely explanation is that the first step of the intermediate-complex mechanism is usually rate-determining, and this step is promoted by groups with strong $-I$ effects. This would explain why fluoro and nitro are such good leaving groups when this mechanism is operating. An alternate explanation has been proposed for the leaving ability of fluorine. According to this, fluorine, the only one of the halogens which can form hydrogen bonds, does form such a bond with the nucleophile.[39] Of course, this can be possible only when the nucleophile contains a hydrogen. Fluoro is the poorest leaving group of the halogens when the second step of the intermediate-complex mechanism is rate-determining (p. 494) or when the benzyne mechanism is operating.

---

[33] Wotiz and Huba, *J. Org. Chem.* **24**, 595 (1959). Eighteen other reactions also gave products predicted by these principles.

[34] Zoltewicz and Bunnett, *J. Am. Chem. Soc.* **87**, 2640 (1965).

[35] Greizerstein, Bonelli, and Brieux, *J. Am. Chem. Soc.* **84**, 1026 (1962); Knowles, Norman, and Prosser, *Proc. Chem. Soc.* **1961**, 341. For a list of σ^- values, see p. 241.

[36] Loudon and Shulman, *J. Chem. Soc.* **1941**, 722; Suhr, *Chem. Ber.* **97**, 3268 (1964).

[37] Kobrina and Yakobson, *J. Gen. Chem. USSR* **33**, 3238 (1963).

[38] Reinheimer, Taylor, and Rohrbaugh, *J. Am. Chem. Soc.* **83**, 835 (1961); Ross, *J. Am. Chem. Soc.* **81**, 2113 (1959); Bunnett, Garbisch, and Pruitt, *J. Am. Chem. Soc.* **79**, 385 (1957); Parker and Read, *J. Chem. Soc.* **1962**, 9, 3149.

[39] Chapman and Parker, *J. Chem. Soc.* **1951**, 3301; Bamkole, Bevan, and Hirst, *Chem. Ind. (London)* **1963**, 119.

The Effect of the Attacking Nucleophile. It is not possible to construct a nucleophilicity order which is invariant, since different substrates and different conditions lead to different orders of nucleophilicity, but an overall approximate order is $NH_2^- > Ph_3C^- > PhNH^-$ (aryne mechanism) $> ArS^- > RO^- > R_2NH > ArO^- > OH^- > ArNH_2 > NH_3 > I^- > Br^- > Cl^- > H_2O >$ ROH.[40] As with aliphatic nucleophilic substitution, nucleophilicity is generally dependent on base strength, and nucleophilicity increases as the attacking atom moves down a column of the periodic table, but there are some surprising exceptions; for example, OH^-, a stronger base than ArO^-, is a poorer nucleophile. In a series of similar nucleophiles, such as substituted anilines,[41] nucleophilicity *is* correlated with base strength. Oddly, the cyanide ion is not a nucleophile for aromatic systems, except for sulfonic acid salts (reaction **3-12**) and in the von Richter (**3-26**) and Rosenmund–von Braun (**3-11**) reactions, which are special cases.

REACTIONS

In the first part of this section, reactions are classified according to attacking species, with all leaving groups considered together, except for hydrogen and N_2^+, which are treated subsequently. Finally, a few rearrangement reactions are discussed.

All Leaving Groups except Hydrogen and N_2^+

A. Oxygen nucleophiles

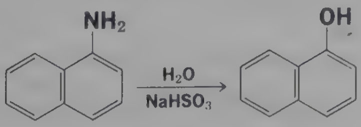
3-1 Replacement by OH

$$ArBr + OH^- \longrightarrow ArOH$$

Aryl halides can be converted to phenols only if activating groups are present or if exceedingly strenuous conditions are employed. Other leaving groups, including nitro, azide, etc., can also be replaced by OH groups. When the reaction is carried out at high temperatures, as in the commercial process for the preparation of phenol from chlorobenzene, cine substitution is observed, indicating a benzyne mechanism.

OS **I**, 455; **II**, 451.

3-2 Replacement of an amino group by a hydroxyl group



The amino group of naphthylamines may be replaced by a hydroxyl group by treatment with aqueous bisulfite.[42] The scope is greatly limited: the amino group (which may be NH_2 or NHR) must be on a naphthalene ring, with very few exceptions. The reaction is reversible (see reaction **3-7**), and both the forward and reverse reactions are called the *Bucherer reaction*. The mechanism is completely different from any outlined in the first section of this chapter and is discussed at reaction **3-7**.

---

[40] This list is compiled from data in Ref. 1, p. 340; Bunnett, Ref. 2, p. 13; Sauer and Huisgen, Ref. 2, p. 311; and Bunnett, *Ann. Rev. Phys. Chem.* **14**, 271–290 (1963).

[41] Sauer and Huisgen, Ref. 2, p. 311. Also see Murto, *Acta Chem. Scand.* **18**, 1043 (1964).

3-3 Alkali fusion of sulfonate salts

$$ArSO_3^- \xrightarrow[300\text{–}320°]{\text{NaOH fusion}} ArO^-$$

Aryl sulfonic acids may be converted, through their salts, to phenols, by alkali fusion. In spite of the extreme conditions, the reaction gives fairly good yields, except when the substrate contains other groups which are attacked by alkali at the fusion temperatures. Milder conditions may be used when the substrate contains activating groups, but the presence of deactivating groups hinders the reaction. The mechanism is obscure, but a benzyne intermediate has been ruled out by the finding that cine substitution does not occur.[42a]

OS **I**, 175; **III**, 288.

3-4 Replacement by OR or OAr

$$ArBr + OR^- \longrightarrow ArOR$$

This reaction is similar to reaction **3-1** and, like that one, requires activated substrates. With unactivated substrates, side reactions predominate. This reaction gives better yields than reaction **3-1** and is used more often. In addition to halides, leaving groups may be nitro, NR_3^+, other OR, etc., even OH.[43] Acid salts, $RCOO^-$, are sometimes used as nucleophiles.

For aroxide nucleophiles, the reaction is promoted by copper salts, and when these are used, activating groups need not be present. This method of preparation of diaryl ethers is called the *Ullmann reaction,* but should not be confused with the more important Ullmann coupling reaction (**3-16**). The reactivity order is typical of nucleophilic substitutions, despite the presence of the copper salts.[44]

OS **I**, 219; **II**, 445; **III**, 293, 566; **45**, 89.

B. Sulfur nucleophiles

3-5 Replacement by SH or SR

$$ArBr + SH^- \longrightarrow ArSH$$

$$ArBr + SR^- \longrightarrow ArSR$$

---

[42] For reviews, see Seeboth, *Angew. Chem. Intern. Ed. Engl.* **6**, 307–317 (1967); Drake, *Org. Reactions* **1**, 106–128 (1942); and Gilbert, "Sulfonation and Related Reactions," pp. 166–169, Interscience Publishers, Inc., New York, 1965.

[42a] Buzbee, *J. Org. Chem.* **31**, 3289 (1966); Oae, Furukawa, Kise, and Kawanishi, *Bull. Chem. Soc. Japan* **39**, 1212 (1966).

[43] Oae and Kiritani, *Bull. Chem. Soc. Japan* **37**, 770 (1964).

[44] Weingarten, *J. Org. Chem.* **29**, 977, 3624 (1964).

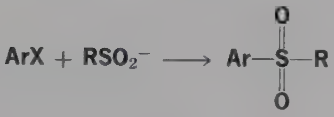
Aryl thiols and thioethers may be prepared in reactions similar to **3-1** and **3-4**. Activated aryl halides generally give good results, but side reactions are occasionally important. Diaryl sulfides may be prepared by the use of SAr^-. Sulfide salts (for example, Na_2S) may also be used to prepare mercaptans, though yields are not high. Even unactivated aryl halides react with SAr^- if amides (e.g., dimethylformamide) are used as solvents,[45] though the mechanism is still nucleophilic substitution.

Other sulfur nucleophiles also react with activated aryl halides:

$$2ArX + S_2^{=} \longrightarrow Ar{-}S{-}S{-}Ar$$

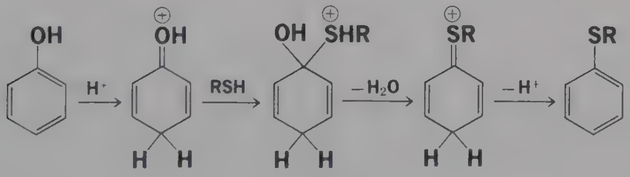
$$ArX + SO_3^{=} \longrightarrow Ar{-}SO_3^-$$

$$ArX + SCN^- \longrightarrow ArSCN$$



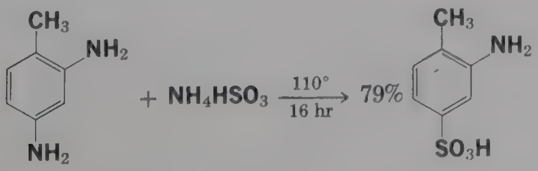
$$ArX + RSO_2^- \longrightarrow Ar{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}{-}R$$

Hydroxyl groups may be replaced by SR groups in acid solution.[46] In this case the mechanism bears certain resemblances to that of the Bucherer reaction (**3-7**):



As with the Bucherer reaction, yields are highest with naphthols (50 to 60%), though in this case phenols also give the reaction (20 to 40% yields).

The reaction between 2,4-diaminotoluene and ammonium hydrogen sulfite has been reported to give replacement of NH_2 by SO_3H:[47]



OS **I**, 220; **III**, 86, 239, 667; **42**, 22; **44**, 47. Also see OS **43**, 97.

[45] Campbell, *J. Org. Chem.* **29**, 1830 (1964).
[46] Oae and Kiritani, *Bull. Chem. Soc. Japan* **38**, 1381 (1965).
[47] Allan and Podstata, *Collection Czech. Chem. Commun.* **30**, 1024 (1965).

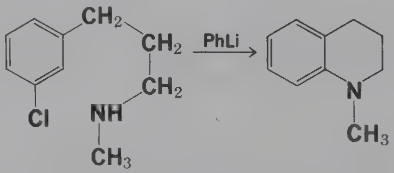
C. Nitrogen nucleophiles

3-6 Replacement by NH_2, NHR, or NR_2

$$ArBr + NH_3 \longrightarrow ArNH_2$$
$$ArBr + RNH_2 \longrightarrow ArNHR$$
$$ArBr + R_2NH \longrightarrow ArNR_2$$

Activated aryl halides react quite well with ammonia and with primary and secondary amines to give the corresponding arylamines. Primary and secondary amines usually give better results than ammonia, with piperidine being especially reactive. Picryl chloride (2,4,6-trinitrochlorobenzene) is often used to form amine derivatives. 2,4-Dinitrofluorobenzene is used to tag the amino end of a peptide or protein chain. Other leaving groups in this reaction may be NO_2, N_3, OSO_2R, OR, and SR.

Nonactivated aryl halides may be converted to amines by the use of $NaNH_2$ or $NaNR_2$.[48] With these reagents, the benzyne mechanism operates, and so cine substitution is often found. Ring closure has been effected by this type of reaction,[49] for example,

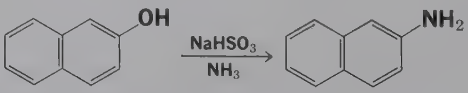


It has proved possible to close larger rings too in this manner: eight- and even twelve-membered. Triarylamines have been prepared in a similar manner, from ArI and Ar'_2NLi, even with unactivated ArI.[50] Sulfonic acid salts may be fused with alkali-metal amides to give aromatic amines, a process similar to reaction **3-3.**

The reaction with ammonia or amines, which undoubtedly proceeds by the intermediate-complex mechanism, is catalyzed by copper salts, though these are normally used only with rather unreactive halides. The manner of catalysis is poorly understood, and it has been suggested that perhaps a free-radical process is involved.

OS **I,** 544; **II,** 15, 221, 228; **III,** 53, 307, 573; **IV,** 52, 336, 364; **40,** 74, 96.

3-7 Replacement of a hydroxy group by an amino group



---

[48] For a review, see Heaney, *Chem. Rev.* **62,** 81–97 (1962), pp. 83–89.

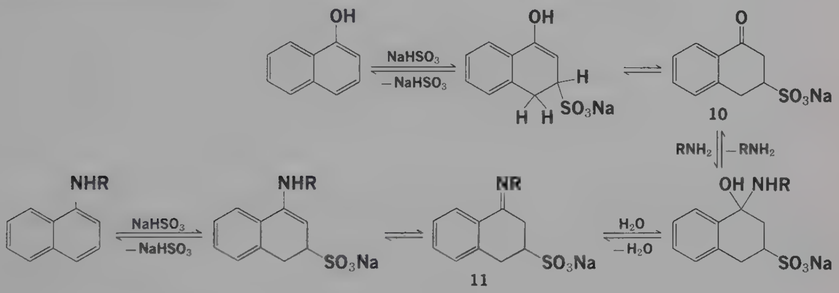
[49] Huisgen, König, and Lepley, *Chem. Ber.* **93,** 1496 (1960); Bunnett and Hrutfiord, *J. Am. Chem. Soc.* **83,** 1691 (1961).

[50] Neunhoeffer and Heitmann, *Chem. Ber.* **94,** 2511 (1961).

The reaction of naphthols with sodium bisulfite is the reverse of reaction **3-2** and has a similar scope. It is also called the *Bucherer reaction.* Primary amines may be used instead of ammonia, in which case N-substituted naphthylamines are obtained. In addition, primary naphthylamines may be converted to secondary, by a transamination reaction:

$$\mathrm{ArNH_2 + RNH_2 \xrightarrow[NaHSO_3]{} ArNHR}$$

The mechanism of the Bucherer reaction amounts to a kind of overall addition-elimination:[51]



The first step in either direction consists of addition of $NaHSO_3$ to one of the double bonds of the ring, giving an enol (or enamine) which tautomerizes to the keto (or imine) form. The conversion of **10** to **11** (or vice versa) is an example of reaction **6-15** (p. 667) (or **6-2,** p. 656). Evidence for this mechanism was the isolation of **10**[52] and the demonstration that, for β-naphthol treated with ammonia and HSO_3^-, the rate of the reaction is dependent only on the substrate and on HSO_3^-, indicating that ammonia is not involved in the rate-determining step.[53] If the starting compound is a β-naphthol, the intermediate is a 2-keto-4-sulfonic acid compound, so that the sulfur of the bisulfite in either case attacks meta to the OH or NH_2.[54]

Hydroxy groups on benzene rings have been replaced by NH_2 or NHR, when the hydroxy group is activated by OH, NH_2, or NHR groups in ortho and para positions.[55] The mechanism here also involves keto intermediates but is not the same as for the Bucherer reaction.

OS **III,** 78.

D. Halogen nucleophiles

3-8 Halide exchange

$$\mathrm{Ar{-}X + X'^- \longrightarrow Ar{-}X' + X^-}$$

It is possible to replace a halogen on a ring by another halogen, if the ring is activated. There is an equilibrium, but it is usually possible to shift this in the desired direction by the use of an excess of added halide ion.[56] Another common leaving group is nitro, which may be replaced with chloro by use of NH_4Cl, PCl_5, $SOCl_2$, HCl, Cl_2, or CCl_4. Some of these reagents operate only at high temperatures, and the mechanism is not always nucleophilic substitution. A phenolic hydroxy group may be replaced by chloro with PCl_5 or $POCl_3$, but only if activated. Unactivated aryl halides give phosphates when treated with $POCl_3$. An example is formation of tricresyl phosphate (TCP):

---

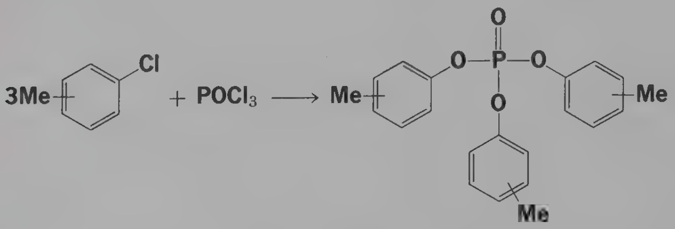
[51] Rieche and Seeboth, *Ann.* **638,** 66 (1960).

[52] Rieche and Seeboth, *Ann.* **638,** 43, 57 (1960).

[53] Kozlov and Veselovskaia, *J. Gen. Chem. USSR* **28,** 3359 (1958).

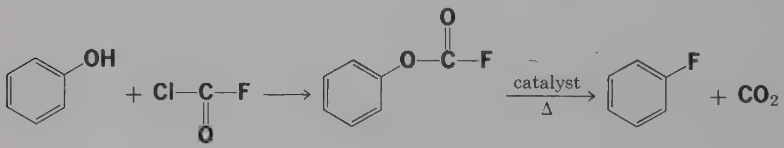
[54] Rieche and Seeboth, *Ann.* **638,** 76 (1960).

[55] Lantz and Michel, *Bull. Soc. chim. France* **1961,** 2402, **1962,** 353, **1964,** 534, 538.

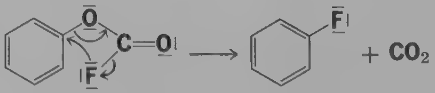


Halide exchange is particularly useful for putting fluorine into a ring, since there are fewer alternate ways of doing this than for the other halogens. Activated aryl chlorides give fluorides when treated with KF in dimethylformamide, dimethyl sulfoxide, or dimethyl sulfone.[57] All six chlorines of hexachlorobenzene may be replaced by F in this manner.[58] Halide exchange may also be accomplished with copper halides. Since the leaving-group order in this case is I > Br > Cl ≫ F, the intermediate-complex mechanism is probably not operating.[59]

An indirect method for the replacement of OH or SH by F has been developed by Christie and Pavlath.[60] The method consists in the treatment of a phenol or thiophenol (or their salts) with COFCl to give a fluoroformate (or fluorothioformate), which is pyrolyzed to the product



Overall yields are high in most cases. An S_Ni mechanism has been proposed for the pyrolysis step:



OS **III**, 194, 272, 475; **40**, 34.

---

[56] Sauer and Huisgen, *Angew. Chem.* **72**, 294–315 (1960), p. 297.

[57] Starr and Finger, *Chem. Ind.* (*London*) **1962**, 1328; Finger, Starr, Dickerson, Gutowsky, and Hamer, *J. Org. Chem.* **28**, 1666 (1963).

[58] Vorozhtsov, Platonov, and Yakobson, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963**, 1389.

[59] Bacon and Hill, *J. Chem. Soc.* **1964**, 1097, 1108.

[60] Christie and Pavlath, *J. Org. Chem.* **30**, 3170, 4104 (1965), **31**, 559 (1966).

E. Hydrogen as nucleophile

3-9 Reduction of phenols and phenolic esters and ethers

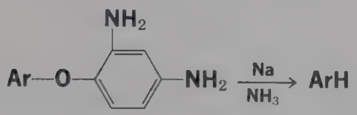
$$\mathrm{ArOH} \xrightarrow{\mathrm{Zn}} \mathrm{ArH}$$

Phenols may be reduced by distillation over zinc dust, or with HI and red phosphorus, but these methods are quite poor and are seldom feasible. Catalytic hydrogenation has also been used, but the corresponding cyclohexanol (see reaction **5-12**, p. 597) is a side product.[61]

Much better results have been obtained by conversion of phenols to certain esters or ethers, and reduction of the latter:[62]

$$\mathrm{Ar{-}O{-}P{-}(OEt)_2} \xrightarrow[\mathrm{NH_3}]{\mathrm{Na}} \mathrm{ArH}$$

$$\mathrm{ArOTs} + \mathrm{NH_2NH_2} \xrightarrow[\mathrm{Pd}]{} \mathrm{ArH}$$

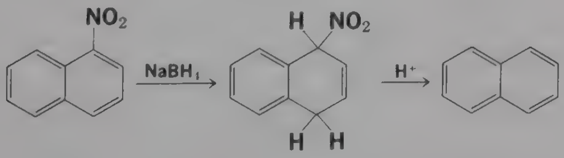


12

12 are prepared by treatment of phenols with 2,4-dinitrofluorobenzene (reaction **3-4**) and reduction of the dinitro product.

3-10 Reduction of halides and nitro compounds. The reaction ArX ⟶ ArH is treated in Chapter 11 (reaction **1-45**, p. 439), though, depending on reagent and conditions, it may be nucleophilic[63] or free-radical[64] substitution, as well as electrophilic.

The nitro group of aromatic nitro compounds has been removed with sodium borohydride.[65] This reaction involves an addition-elimination mechanism, in which the addition is 1,4:



The first step is similar to the Birch reduction (reaction **5-12**, p. 597).

---

[61] Shuikin and Erivanskaya, *Russ. Chem. Rev.* **29**, 309–320 (1960), pp. 313–315.

[62] References for these methods are, in the order given: Kenner and Williams, *J. Chem. Soc.* **1955**, 522, and Pelletier and Locke, *J. Org. Chem.* **23**, 131 (1958); Kenner and Murray, *J. Chem. Soc.* **1949**, S178, and Rottendorf and Sternhell, *Australian J. Chem.* **16**, 647 (1963); Sawa, Tsuji, and Maeda, *Tetrahedron* **15**, 144, 154 (1961), and Pirkle and Zabriskie, *J. Org. Chem.* **29**, 3124 (1964).

[63] For example, see Corbett and Holt, *J. Chem. Soc.* **1963**, 2385.

[64] Menapace and Kuivila, *J. Am. Chem. Soc.* **86**, 3047 (1964).

[65] Severin, Schmitz, and Temme, *Chem. Ber.* **96**, 2499 (1963).

F. Carbon nucleophiles

3-11 Replacement of halides by cyanide. The Rosenmund-von Braun reaction

$$\mathrm{ArBr} + \text{anhyd. } \mathrm{CuCN} \xrightarrow{200^\circ} \mathrm{ArCN}$$

The reaction between aryl halides and cuprous cyanide is called the *Rosenmund–von Braun reaction.*[66] The mechanism is not certain and may not be nucleophilic substitution. However, it is possible that the copper complexes with the halide, allowing CN^- to attack. Other cyanides, for example, KCN and NaCN, do not react with aryl halides, even activated ones.

OS **III**, 212, 631.

3-12 Cyanide fusion of sulfonate salts[67]

$$\mathrm{ArSO_3^-} \xrightarrow{\text{NaCN fusion}} \mathrm{ArCN}$$

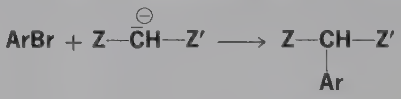
This reaction is very similar to reaction **3-3.** Yields are usually low.

3-13 Coupling of organometallic compounds with aryl ethers

$$\mathrm{ArOR} + \mathrm{R'MgX} \longrightarrow \mathrm{ArR'}$$

Aryl halides, even when activated, generally do not couple with Grignard reagents. The reaction proceeds better when OR can be the leaving group, providing that activating groups are present in the ring. C_6F_6 with methylmagnesium iodide gave only 3% C_6F_5Me, but with alkyllithiums good yields of C_6F_5R were obtained.[68]

3-14 Arylation at a carbon containing an active hydrogen



$$\mathrm{ArBr} + \mathrm{Z{-}\overset{\ominus}{\bar{C}}H{-}Z'} \longrightarrow \mathrm{Z{-}\underset{\displaystyle Ar}{\underset{|}{C}}H{-}Z'}$$

The arylation of compounds of the form ZCH_2Z' is analogous to reaction **0-86** (p. 357), and Z is as defined there. Activated aryl halides generally give good results. Even unactivated aryl halides may be employed, if the reaction is carried out in the presence of excess sodium amide.[69] Compounds of the form ZCH_2Z' and even simple ketones and esters have been arylated in this manner. The reaction with unactivated halides proceeds by the benzyne mechanism, and represents a method for extending the malonic ester (and similar) syntheses to aromatic compounds. The base performs two functions: it removes a proton from ZCH_2Z' and catalyzes the benzyne mechanism.

---

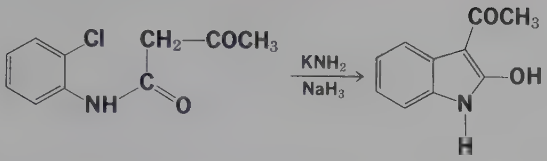
[66] For a review, see Mowry, *Chem. Rev.* **42,** 189–283 (1948), pp. 207–209.

[67] For a review, see Ref. 66, pp. 193–194.

[68] Birchall and Haszeldine, *J. Chem. Soc.* **1961,** 3719.

[69] Leake and Levine, *J. Am. Chem. Soc.* **81,** 1169, 1627 (1959).

The reaction has been used for ring closure:[70]



Diaryliodonium salts have also been used to arylate ZCH_2Z', but the mechanism is apparently free-radical.[71]

Aryl iodides (even unactivated) react with copper acetylides to give arylacetylenes.[72] The mechanism in this case may also be free-radical.

OS **40,** 1.

3-15 Carbalkoxylation

$$\mathrm{ArI} \xrightarrow[\mathrm{Ni(CO)_4}]{\mathrm{ROH}} \mathrm{ArCOOR}$$

Aryl iodides may be converted directly to esters by treatment with nickel carbonyl in ROH as solvent.[73] The yields are nearly quantitative. In aprotic solvents, such as tetrahydrofuran, the products are benzils, ArCOCOAr. The reaction is not successful for aryl chlorides, bromides, or fluorides.

3-16 The Ullmann reaction

$$2\mathrm{ArI} \xrightarrow{\mathrm{Cu}} \mathrm{Ar{-}Ar}$$

The coupling of aryl halides with copper is called the *Ullmann reaction.*[74] The reaction is of broad scope and has been used to prepare many symmetrical and unsymmetrical biaryls. When a mixture of two different aryl halides is used, there are three possible products, but often only one of these is obtained. For example, picryl chloride and iodobenzene gave only 2,4,6-trinitrobiphenyl.[75] The best leaving group is iodo, and the reaction is most often done on aryl iodides, but bromides, chlorides, and even thiocyanates have been used.

The effects of other groups on the ring are unusual. The nitro group is strongly activating, but only in the ortho, not in the meta and para, positions.[76] R and OR activate in all positions. Not only do OH, NH_2, NHR, and NHCOR inhibit the reaction, as would be expected for aromatic nucleophilic substitution, but so do COOH (but not COOR), SO_2NH_2, and similar groups, for which the reaction fails completely. These groups inhibit the coupling reaction by causing side reactions.

---

[70] Bunnett and Hrutfiord, *J. Am. Chem. Soc.* **83,** 1691 (1961); Bunnett, Kato, Flynn, and Skorcz, *J. Org. Chem.* **28,** 1 (1963).

[71] Hampton, Harris, and Hauser, *J. Org. Chem.* **29,** 3511 (1964).

[72] Castro and Stephens, *J. Org. Chem.* **28,** 2163 (1963); Stephens and Castro, *J. Org. Chem.* **28,** 3313 (1963).

[73] Bauld, *Tetrahedron Letters* **1963,** 1841.

[74] For reviews, see Fanta, *Chem. Rev.* **38,** 139–196 (1946), **64,** 613–632 (1964); and Bacon and Hill, *Quart. Rev.* (*London*) **19,** 95–125 (1965), pp. 101–107.

[75] Rule and Smith, *J. Chem. Soc.* **1937,** 1096.

[76] Forrest, *J. Chem. Soc.* **1960,** 592.

The mechanism is not known with certainty.[77] Many have argued that it is of the free-radical type, and there is some evidence for this view, but the bulk of the evidence is against it: iodobenzene gives biphenyl free from polymer; when the reaction is carried out in nitrobenzene, no nitrobiphenyl is obtained; and the best yields of unsymmetrical products are obtained by reaction of an activated halide with an unreactive one at a temperature too low for the unreactive halide to react with copper by itself. The mechanism is probably similar to that of the Wurtz reaction (**0-81**, p. 353):

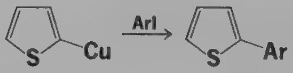
$$1. \qquad \text{ArI} + \text{Cu} \longrightarrow \text{ArCuI}$$

$$2. \qquad \text{ArCuI} + \text{ArI} \longrightarrow \text{ArAr}$$

A possible alternative second step is

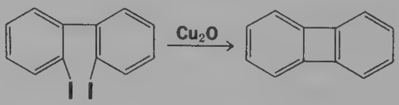
$$2\text{ArCuI} \longrightarrow \text{ArAr} + \text{Cu} + \text{CuI}$$

The species represented as ArCuI may not actually have this structure, but some kind of a complex is formed. Organocopper compounds have been trapped by coordination with organic bases.[78] In addition, 2-thienylcopper has been independently prepared and, treated with aryl iodides, gives 2-arylthiophenes:[79]



The fact that iodo is the best leaving group suggests that iodides undergo step 1 more readily than the other halides.

A similar reaction has been used for ring closure:[80]



Since copper itself is not effective in this case, the mechanism is probably different.

Ullmann-type coupling has also been carried out with ArNa and Ar′Cl. This proceeds by the benzyne mechanism.[81]

OS **III**, 339; **40**, 105.

---

[77] Forrest, *J. Chem. Soc.* **1960**, 594.

[78] Lewin and Cohen, *Tetrahedron Letters* **1965**, 4531.

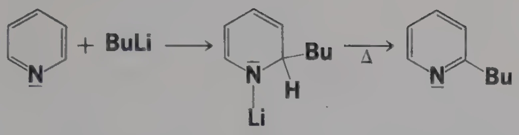
[79] Nilsson, *Tetrahedron Letters* **1966**, 675.

[80] For a discussion, see Fanta, *Chem. Rev.* **64**, 613–632 (1964), p. 623.

[81] Ehrhart, *Chem. Ber.* **96**, 2042 (1963).

Hydrogen as Leaving Group

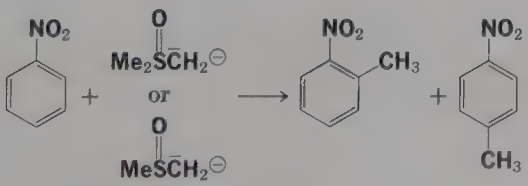
3-17 Alkylation and arylation



The alkylation of heterocyclic nitrogen compounds with alkyllithiums is called *Ziegler alkylation.* Aryllithiums give arylation. The reaction occurs by an addition-elimination mechanism, and the adduct can be isolated. Upon heating of the adduct, elimination of LiH occurs (see reaction **7-18,** p. 767), and an alkylated product is obtained. With respect to the 2-carbon the first step is the same as that of the intermediate-complex mechanism. The difference is that the unshared pair of electrons on the nitrogen combines with the lithium, so that the extra pair of ring electrons has a place to go: it becomes the new unshared pair on the nitrogen.

The reaction has been applied to nonheterocyclic aromatic compounds: benzene, naphthalene, and phenanthrene have been alkylated with alkyllithiums, though the usual reaction with these reagents is **2-12** (p. 468);[82] and Grignard reagents have been used to alkylate naphthalene.[83] The addition-elimination mechanism apparently applies in the latter case.

Aromatic nitro compounds may be methylated by treatment with dimethyloxosulfonium methylide[84] or the methylsulfinyl carbanion (obtained by treatment of dimethyl sulfoxide with a strong base):[85]



The latter reagent also methylates certain heterocyclic compounds (e.g., quinoline) and certain fused aromatic compounds (e.g., anthracene, phenanthrene).[86] The reactions with the sulfur carbanions are especially useful, since none of these substrates can be methylated by the Friedel-Crafts procedure (reaction **1-12,** p. 406).

OS **II,** 517.

---

[82] Dixon and Fishman, *J. Am. Chem. Soc.* **85,** 1356 (1963).

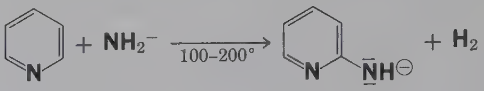
[83] Bryce-Smith and Wakefield, *Tetrahedron Letters* **1964,** 3295.

[84] Traynelis and McSweeney, *J. Org. Chem.* **31,** 243 (1966).

[85] Russell and Weiner, *J. Org. Chem.* **31,** 248 (1966).

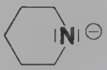
[86] Ref. 85; Argabright, Hofmann, and Schriesheim, *J. Org. Chem.* **30,** 3233 (1965); Nozaki, Yamamoto, and Noyori, *Tetrahedron Letters* **1966,** 1123.

3-18 Amination of heterocyclic nitrogen compounds



Pyridine and other heterocyclic nitrogen compounds can be aminated with alkali-metal amides, in a process called the *Chichibabin reaction.*[87] The attack is always ortho to the nitrogen, unless both positions are filled, in which case para attack occurs. Nitro compounds do not give the reaction.

Substituted alkali-metal amides, for example, **13**, have also been used. Free amines may give the reaction, but only in the presence of bases like KOH.[88] Very likely the amide ion is the actual nucleophile in these cases.



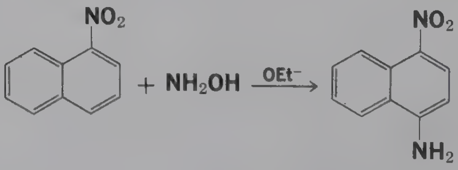
13

Apparently the hydride ion which is the leaving group combines with a proton from the initial $ArNH_2$ product to give H_2. At lower temperatures, in ammonia, potassium nitrate is sometimes necessary to oxidize the hydride ion. The mechanism may be similar to that of reaction **3-17.** A pyridyne intermediate was ruled out by the observations that deuterium is not lost from pyridine-3-*d*,[89] and that 3-ethylpyridine gave 2-amino-3-ethylpyridine.[90]

Analogous reactions have been carried out with hydrazide ions, $R_2N\bar{N}H^-$.[91]

There are no *Organic Syntheses* references, but see OS **43,** 97, for a related reaction.

3-19 Amination by hydroxylamine



Activated aromatic compounds can be directly aminated with hydroxylamine, in the presence of strong bases. Conditions are mild, and yields are high. Ions of the type **14** are intermediates

---

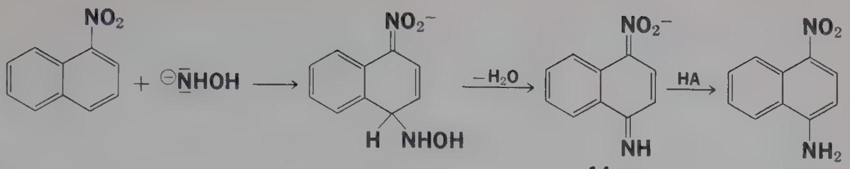
[87] For a review, see Leffler, *Org. Reactions* **1,** 91–104 (1942).

[88] Bradley and Williams, *J. Chem. Soc.* **1959,** 360.

[89] Abramovitch, Helmer, and Saha, *Can. J. Chem.* **43,** 725 (1965).

[90] Ban and Wakamatsu, *Chem. Ind. (London)* **1964,** 710.

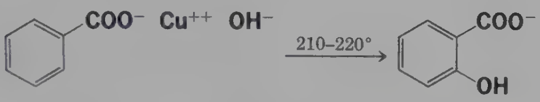
[91] Kauffmann, Hansen, Kosel, and Schoeneck, *Ann.* **656,** 103 (1962).



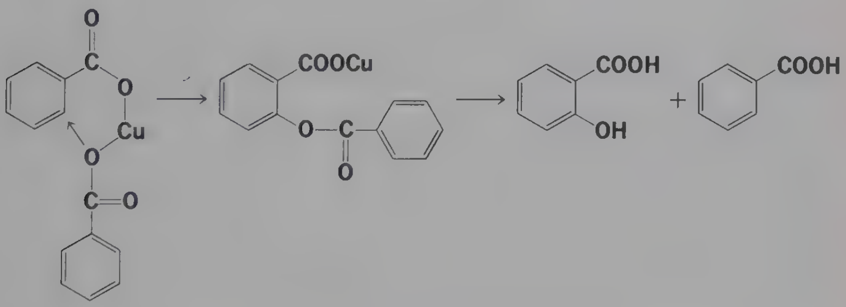
14

OS **III**, 664.

3-20 Hydroxylation of aromatic acids



When basic copper salts of aromatic acids are heated, hydroxylation occurs in the ortho position.[92] Better results are obtained by heating cupric carboxylates in protic solvents.[93] In the latter case there is a cyclic process leading to an ester intermediate:



Phenols are also produced, by concomitant decarboxylation of the salicylic acids or their esters.

N_2^+ as Leaving Group. The diazonium group may be replaced by a number of groups. Most of these are nucleophilic substitutions, with S_N1 mechanisms (p. 491), but some are free-radical reactions and are treated in Chapter 14. (For *formation* of diazonium ions, see reaction **2-33**, p. 484.) The N_2^+ group may be replaced by Cl^-, Br^-, and CN^-, by a nucleophilic mechanism (see OS **IV**, 182), but the Sandmeyer reaction is much more useful (reactions **4-18** and **4-20**, p. 554). As was mentioned on page 495, it must always be kept in mind that the N_2^+ group may activate the removal of another group on the ring.

---

[92] Kaeding and Shulgin, *J. Org. Chem.* **27**, 3551 (1962).

[93] Kaeding and Collins, *J. Org. Chem.* **30**, 3750 (1965).

3-21 Replacement by OH

$$ArN_2^+ + H_2O \longrightarrow ArOH$$

Water is usually present whenever diazonium salts are made, but at these temperatures (0 to 5°) the reaction proceeds very slowly. When it is *desired* to have OH replace the diazonium group, the excess nitrous acid is destroyed, and the solution is usually boiled. Some diazonium salts require even more vigorous treatment, e.g., boiling with aqueous sulfuric acid. The reaction may be performed on solutions of any diazonium salts, but hydrosulfates are preferred to chlorides or nitrates, since in these cases there is competition from the nucleophiles Cl^- or NO_3^-.

OS **I,** 404; **III,** 130, 453, 564.

3-22 Replacement by sulfur-containing groups

$$ArN_2^+ + HS^- \longrightarrow ArSH$$

$$ArN_2^+ + S^{=} \longrightarrow ArSAr$$

$$ArN_2^+ + RS^- \longrightarrow ArSR$$

$$ArN_2^+ + SCN^- \longrightarrow ArSCN + ArNCS$$

These reactions represent a convenient method of putting sulfur-containing groups onto an aromatic ring. With $Ar'S^-$ attack at the nitrogen takes precedence, so that the product is a diazosulfide (Ar—N═N—S—Ar').[94] Thiophenols can be made as shown above, but more often the diazonium ion is treated with EtO—CSS⁻ or $S_2^{=}$, which give the expected products, and these are easily convertible to thiophenols.

OS **II,** 580; **III,** 809. Also see OS **II,** 238.

3-23 Replacement by iodine

$$ArN_2^+ + I^- \longrightarrow ArI$$

One of the best methods for the introduction of iodine into aromatic rings is the reaction of diazonium salts with iodide ions. Analogous reactions with chloride, bromide, and fluoride ions give poorer results, and reactions **4-18** (p. 554) and **3-24** are preferred for the preparation of aryl chlorides, bromides, and fluorides. However, when other diazonium reactions are carried out in the presence of these ions, halides are usually side products.

The actual attacking species is probably not only I^-, if it is that at all. The iodide ion is oxidized (by the diazonium ion, or nitrous acid, or some other oxidizing agent) to iodine, which in a solution containing iodide ions is converted to I_3^-, and this is the actual attacking species, at least partly. This was shown by isolation of $ArN_2^+ \quad I_3^-$ salts, which, on standing, gave ArI.[95] From this, it may be inferred that the reason the other halide ions give poor results, is not that they are poor nucleophiles, but that they are poor reducing agents (compared to iodide).

---

[94] Price and Tsunawaki, *J. Org. Chem.* **28,** 1867 (1963).

[95] Carey, Jones, and Millar, *Chem. Ind.* (*London*) **1959,** 1018; Carey and Millar, *Chem. Ind.* (*London*) **1960,** 97.

OS **II**, 351, 355, 604; **40**, 105.

3-24 Replacement by fluorine. The Schiemann reaction

$$ArN_2^+ \quad BF_4^- \xrightarrow[\Delta]{} ArF + N_2 + BF_3$$

Heating of diazonium fluoborates (the *Schiemann reaction*) is by far the best way of introducing fluorine into an aromatic ring.[96] In the most common procedure, the fluoborate salts are prepared by diazotizing as usual with nitrous acid and HCl and then adding a cold aqueous solution of $NaBF_4$, HBF_4, or NH_4BF_4. A precipitate forms, which is then dried, and the salt is heated in the dry state. These salts are unusually stable for diazonium salts, and the reaction is usually quite successful. In general, any aromatic amine which can be diazotized will form a BF_4^- salt, usually with high yields. The diazonium fluoborates can be formed directly from primary aromatic amines and $NOBF_4$.[97] The reaction has also been carried out on $ArN_2^+ \quad PF_6^-$ salts, in some cases with better yields.[98] The reaction has been extended to $ArN_2^+ \quad BCl_4^-$ and $ArN_2^+ \quad BBr_4^-$,[99] but aryl chlorides and bromides are more commonly prepared by the Sandmeyer reaction (**4-18**, p. 554).

The mechanism is of the S_N1 type. That phenyl cations are intermediates was shown by the following experiments: aryl diazonium chlorides are known to arylate other aromatic rings by a free-radical mechanism (see reaction **4-15**, p. 550). In radical arylation it does not matter whether the other ring contains electron-withdrawing or electron-donating groups; in either case a mixture of isomers is obtained, since the attack is not by a charged species. If a phenyl free radical were an intermediate in the Schiemann reaction, then, if the reaction were run in the presence of other rings, it should not matter what kinds of groups were on these other rings: mixtures of biaryls should be obtained in all cases. But if a phenyl cation is an intermediate in the Schiemann reaction, then compounds containing meta-directing groups (that is, meta-directing for *electrophilic* substitutions) should be meta arylated, and those containing ortho-para-directing groups should be ortho and para arylated, since a phenyl cation should behave in this respect like any electrophile (see Chapter 11). Experiments have shown[100] that such orientation is observed, demonstrating that the Schiemann reaction has a positively charged intermediate.

OS **II**, 188, 295, 299; **43**, 12.

3-25 Replacement by hydrogen

$$ArN_2^+ + H_3PO_2 \longrightarrow ArH$$

Reduction of the diazonium group provides an indirect method for the removal of an amino group from a ring. The best and most common way of accomplishing this is by use of H_3PO_2,[101] although many other reducing agents have also been used, among them ethanol, alkaline formaldehyde, and sodium stannite. Ethanol was the earliest reagent used, and it frequently gives good yields, but often ethers, ArOEt, are side products. When hypophosphorous acid (H_3PO_2) is used, then 5 to 15 moles of this reagent are required per mole of substrate. Diazonium salts can be reduced in nonaqueous media by isolation as the BF_4^- salt, and reduction of this with $NaBH_4$ in dimethylformamide.[102]

---

[96] For a review, see Roe, *Org. Reactions* **5**, 193–228 (1949).

[97] Yacobson, D'yachenko, and Bel'chikova, *J. Gen. Chem. USSR* **32**, 842 (1962).

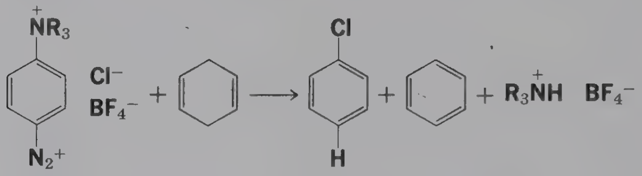
[98] Rutherford, Redmond, and Rigamonti, *J. Org. Chem.* **26**, 5149 (1961).

[99] Olah and Tolgyesi, *J. Org. Chem.* **26**, 2053 (1961).

[100] Makarova and Matveeva, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1958**, 548; Makarova and Gribchenko, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1958**, 672; Makarova, Matveeva, and Gribchenko, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1958**, 1399.

Not many investigations of the identity of the attacking species have been carried out, but it is very likely H^-. It was shown by tritium labeling that, when ethanol or methanol is the reducing agent, it is the α hydrogen of the alcohol which goes into the ring.[103] The alcohols are converted to the corresponding aldehydes. It is known that this usually occurs by a process in which H^- is lost from the α position and H^+ from the oxygen.

In the special case of substrates such as **15**, reducing agents contribute both H^- and H^+:



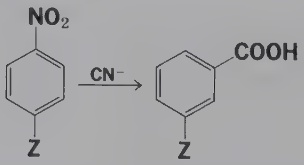
15

The H^- reduces the diazonium group, and chloride displaces the NR_3 group, which combines with H^+ from the reducing agent.[104] Ethanol may also be used for this purpose. This is not a free-radical process, since the addition of a trace of copper converts it to a free-radical process, with different products.

OS **I**, 133, 415; **II**, 353, 592; **III**, 295; **IV**, 947.

Rearrangements

3-26 The von Richter rearrangement



When aromatic nitro compounds are treated with cyanide ion, the nitro group is displaced and a carboxyl group enters, but the carboxyl group does not take the place vacated by the nitro, as determined by analyses of products obtained from substituted nitrobenzenes. The carboxyl group always appears ortho to the displaced nitro group, never meta or para. This is thus a cine substitution (p. 493). The scope of this reaction, called the *von Richter rearrangement,* is variable. As with other nucleophilic aromatic substitutions, the reaction gives best results when electron-withdrawing groups are in ortho and para positions, but yields are low, usually less than 20% and never more than 50%.

---

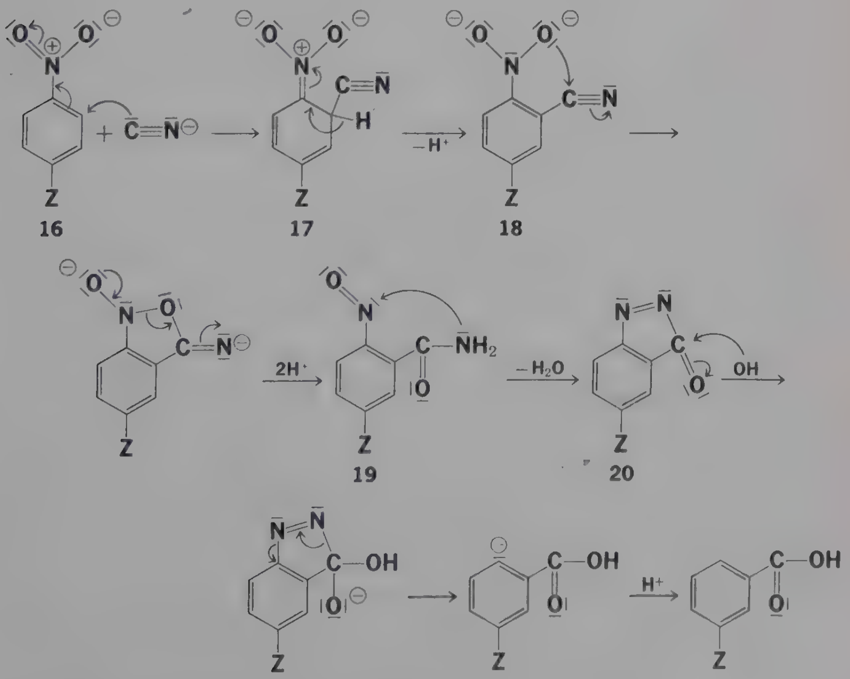
[101] For reviews, see Kornblum, *Org. Reactions* **2**, 262–340 (1944); Belov and Kozlov, *Russ. Chem. Rev.* **32**, 59–75 (1963), pp. 65–66.

[102] Hendrickson, *J. Am. Chem. Soc.* **83**, 1251 (1961).

[103] Melander, *Arkiv Kemi* **3**, 525 (1951).

[104] Meerwein, Wunderlich, and Zenner, *Angew. Chem. Intern. Ed. Engl.* **1**, 613 (1962).

For many years, it was believed that a nitrile, ArCN, was an intermediate, since cyanide is the reagent and nitriles are hydrolyzable to carboxylic acids under the reaction conditions (reaction **6-5**, p. 660). However, in recent years, a remarkable series of results have shown this belief to be in error. Bunnett and Rauhut demonstrated[105] that α-naphthyl cyanide is *not* hydrolyzable to α-naphthoic acid under conditions at which β-nitronaphthalene undergoes the von Richter rearrangement to give α-naphthoic acid. This proved that the nitrile cannot be an intermediate in this case and cast doubt on all other cases, since it is unlikely that different mechanisms would be operating. It was subsequently demonstrated that *elemental nitrogen* is a major product of the reaction.[106] It had previously been assumed that all of the nitrogen in the reaction was converted to ammonia, which would be compatible with a nitrile intermediate, since ammonia is a hydrolysis product of nitriles. At the same time it was shown that NO_2^- is not a major product. The discovery of nitrogen indicated that a nitrogen-nitrogen bond must be formed during the course of the reaction. A mechanism in accord with all the facts was proposed by Rosenblum:[106]

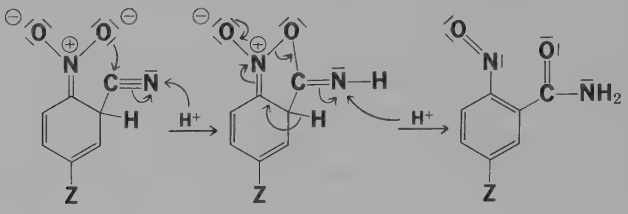


---

[105] Bunnett and Rauhut, *J. Org. Chem.* **21**, 934, 944 (1956).

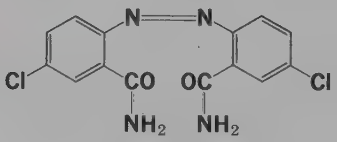
[106] Rosenblum, *J. Am. Chem. Soc.* **82**, 3796 (1960).

It may be remarked that this mechanism postulates as an intermediate at least one stable compound, **19**, and perhaps another (**20**). It also postulates the existence of **18**, which has the unusual functional group $—NO_2=$. It is possible that **19** could be formed without going through **18**:[107]



17 19

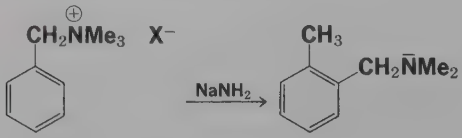
if the attack of the oxygen at the cyano carbon occurs *before* the proton leaves the ring and if another proton attacks the nitrogen as the ring proton is leaving. Since **19** are stable compounds, it should be possible to prepare them independently and subject them to the conditions of the von Richter rearrangement. This has been done, and the correct products are obtained.[108] Further evidence for the mechanism is as follows: among the side products isolated from reaction of **16** (Z = Cl) was **21**, which could arise from reduction of **19**;[109] **20** (Z = H) was prepared, though not isolated, and treatment with cyanide gave nitrogen and benzoic acid;[110] and when **16** (Z = Cl or Br) was treated with cyanide in $H_2{}^{18}O$, one-half of the oxygen in the product was labeled, showing that one of the oxygens of the carboxyl group came from the nitro group and one from the solvent, as required by this mechanism.[111]



21

OS **IV**, 114.

3-27 The Sommelet-Hauser rearrangement

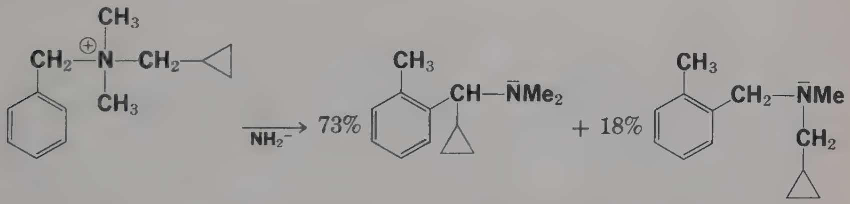


---

[107] Cullen and L'Ecuyer, *Can. J. Chem.* **39**, 862 (1961).
[108] Ibne-Rasa and Koubek, *J. Org. Chem.* **28**, 3240 (1963).
[109] Cullen and L'Écuyer, *Can. J. Chem.* **39**, 144, 155, 382 (1961).
[110] Ullman and Bartkus, *Chem. Ind. (London)* **1962**, 93.
[111] Samuel, *J. Chem. Soc.* **1960**, 1318.

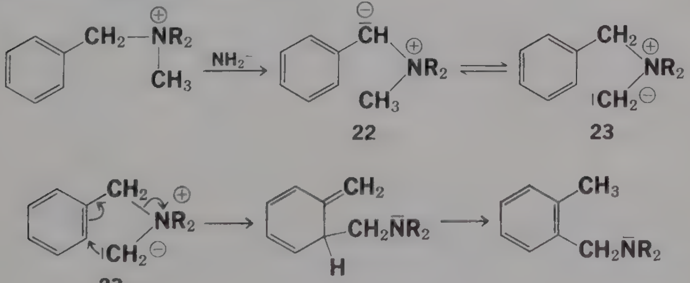
Benzyl quaternary ammonium salts, when treated with alkali-metal amides, undergo a rearrangement which some call the *Sommelet rearrangement* and others the *Hauser rearrangement*.[112] Since both of these men were important in our present knowledge of this reaction, we shall use the joint name adopted by Bumgardner.[113] Since the product is a benzyl tertiary amine, it can be further alkylated, and the product again subjected to the rearrangement. This process may be continued around the ring until an ortho position is blocked.[114]

The rearrangement occurs with high yields, and can be performed with various groups present in the ring.[115] The reaction is most often carried out with three methyl groups on the nitrogen, but other groups may also be used. When the three groups are not the same, competing products may be obtained, for example,[113]



In any case, the Stevens rearrangement (reaction **8-22**, p. 825) is a competing process.

The mechanism is as follows:



22 **23** **23**

The benzyl hydrogen is most acidic and is the one which first loses a proton to give **22**. However, **23**, which is present in smaller amount, is the species which undergoes the rearrangement, shifting the equilibrium in its favor. This mechanism has been called an S_Ni' mechanism. Another mechanism which might be proposed is one in which a methyl group actually breaks away (in some form) from the nitrogen and then attaches itself to the ring.

---

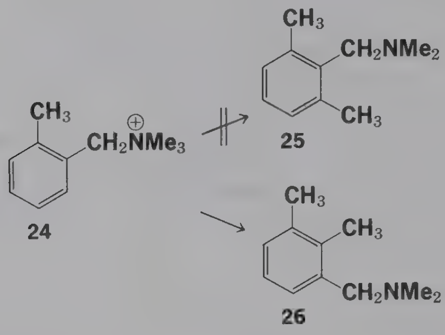
[112] For a review, see Zimmerman, in Mayo, "Molecular Rearrangements," pp. 382–391, Interscience Publishers, Inc., New York, 1963.

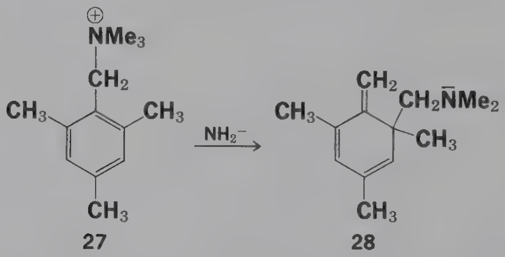
[113] Bumgardner, *J. Am. Chem. Soc.* **85**, 73 (1963).

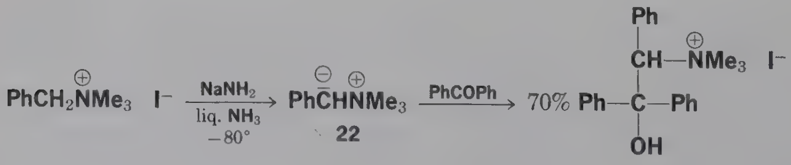
[114] Beard and Hauser, *J. Org. Chem.* **25**, 334 (1960).

[115] Beard and Hauser, *J. Org. Chem.* **26**, 371 (1961); Vaulx, Jones, and Hauser, *J. Org. Chem.* **27**, 4385 (1962); Jones, Beard, and Hauser, *J. Org. Chem.* **28**, 199 (1963).

That this is not so was shown by a product study and by labeling experiments. If the second mechanism were true, then **24** should give **25**, but the former mechanism predicts the formation of **26**, which is what was actually obtained.[116] In the labeling experiments, benzyltrimethylamine, labeled with ^{14}C in the α position of the benzyl group, gave a product labeled in the ring-methyl group, as predicted by the first mechanism, and not in the methylene, as required by the second.[117] Further evidence for the cyclic mechanism was the isolation of **28**, from reaction of **27**.[118] Since **27** is substituted in both ortho positions, it could not give the normal rearrangement product, but the first step of the mechanism *has* occurred. The intermediate **22** has been trapped at −80° by treatment with benzophenone:[119]







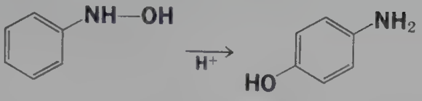
$$\mathrm{PhCH_2\overset{\oplus}{N}Me_3\ I^-}\xrightarrow[\text{liq. NH}_3,\ -80^\circ]{\mathrm{NaNH_2}}\underset{\mathbf{22}}{\mathrm{Ph\overset{\ominus}{C}H\overset{\oplus}{N}Me_3}}\xrightarrow{\mathrm{PhCOPh}} 70\%\ \mathrm{Ph{-}}\underset{\mathrm{OH}}{\overset{\overset{\mathrm{Ph}}{\mathrm{C}}\mathrm{H}-\overset{\oplus}{\mathrm{N}}\mathrm{Me_3}\ \mathrm{I^-}}{\mathrm{C}}}\mathrm{{-}Ph}$$

OS **IV**, 585.

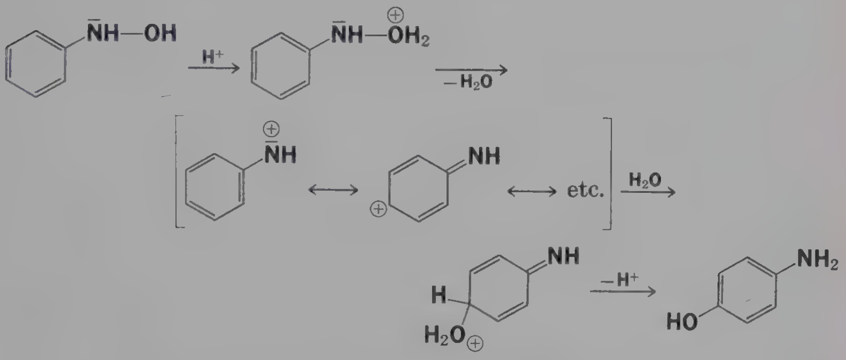
---

[116] Kantor and Hauser, *J. Am. Chem. Soc.* **73**, 4122 (1951).
[117] Jones and Hauser, *J. Org. Chem.* **26**, 2979 (1961).
[118] Hauser and Van Eenam, *J. Am. Chem. Soc.* **79**, 5512 (1957).
[119] Puterbaugh and Hauser, *J. Am. Chem. Soc.* **86**, 1105 (1964).

3-28 Rearrangement of aryl hydroxylamines



Aryl hydroxylamines, treated with acids, rearrange to aminophenols.[120] Although this is similar in appearance to reactions **1-33** to **1-37** (p. 430), the attack on the ring is not electrophilic but nucleophilic. The rearrangement is intermolecular, with the following mechanism:

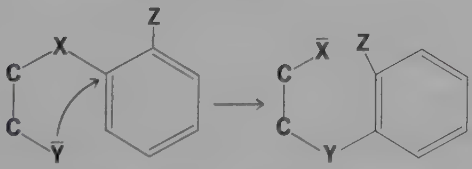


29

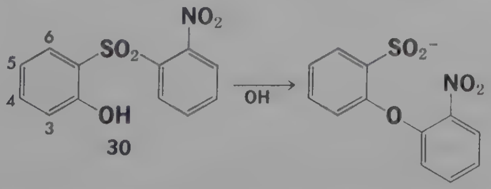
Among the evidence for this mechanism are the facts that other products are obtained when the reaction is run in the presence of competing nucleophiles—e.g., *p*-ethoxyaniline when ethanol is present—and that, when the para position is blocked, compounds similar to **29** are isolated.[120]

OS **IV**, 148.

3-29 The Smiles rearrangement



The *Smiles rearrangement* actually comprises a group of rearrangements which follow the pattern given above.[121] A specific example is



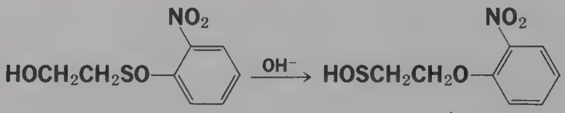
30

---

[120] For a review, see Hughes and Ingold, *Quart. Rev. (London)* **6**, 34–62 (1952), pp. 45–48.

[121] For a review, see Bunnett and Zahler, *Chem. Rev.* **49**, 273–412 (1951), pp. 362–372.

Smiles rearrangements are simply intramolecular nucleophilic substitutions. In the example given, SO_2Ar is the leaving group, ArO^- the nucleophile, and the nitro group serves to activate its ortho position. The ring at which the substitution takes place is nearly always activated, usually by ortho or para nitro groups. X is usually S, SO, SO_2, O, or COO. Y is usually the conjugate base of OH, NH_2, NHR, or SH. The reaction has even been carried out with Y = CH_2^- (phenyllithium was the base here).[122] The reaction rate is greatly enhanced by substitution in the 6-position of the attacking ring, for steric reasons. For example, a methyl, chloro, or bromo group in the 6-position of **30** caused the rate to be about 10^5 times faster than when the same groups were in the 4-position,[123] though electrical effects should be similar at these positions. Although the Smiles rearrangement is usually carried out on compounds containing two rings, this need not be the case. For example,[124]



31

In this case the sulfenic acid (**31**) is unstable, and the actual products isolated were the corresponding sulfinic acid (RSO_2H) and disulfide (R_2S_2).

---

[122] Truce and Ray, *J. Am. Chem. Soc.* **81**, 481 (1959).
[123] Bunnett and Okamoto, *J. Am. Chem. Soc.* **78**, 5363 (1956).
[124] Kent and Smiles, *J. Chem. Soc.* **1934**, 422.

CHAPTER FOURTEEN
Free-radical Substitution

MECHANISMS

Free-radical Mechanisms in General.[1] Any free-radical process must consist of at least two steps. The first step involves the *formation* of free radicals, nearly always by homolytic cleavage of a bond, that is, a cleavage in which each fragment retains one electron:

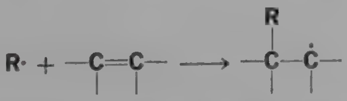
$$\mathbf{A{-}B} \longrightarrow \mathbf{A\cdot} + \mathbf{B\cdot}$$

This is called an *initiation* step, and it may happen spontaneously or may have to be induced by heat or light (see the discussion on p. 156), depending on the type of bond. Peroxides, including hydrogen peroxide, dialkyl, diacyl, and alkyl acyl peroxides, and peracids are the most common source of free radicals induced spontaneously or by heat, but other organic compounds with low-energy bonds, such as azo compounds and disulfides, are also used. Molecules which are cleaved by light are most often chlorine, bromine, and various ketones.

The second necessary step involves the *destruction* of free radicals, and this usually happens by a process opposite to the first, namely, a combination of two like or unlike radicals to form a new bond:

$$\mathbf{A\cdot} + \mathbf{B\cdot} \longrightarrow \mathbf{A{-}B}$$

This type of step is called *termination,*[2] and it ends the reaction as far as these particular radicals are concerned, unless the bond is broken once again and a new round begins.[3] However, it is not often that termination follows *directly* upon initiation. The reason for this is that most radicals are very reactive and will react with the first available species with which they come in contact, and in the usual situation, in which the concentration of radicals is low, this is much more likely to be a molecule than another radical. When a radical (which has an odd number of electrons) reacts with a molecule (which has an even number), then the products must have a total number of electrons which is odd. The product in a particular step of this kind may be one particle, e.g.,



$$\mathrm{R\cdot} + {-}\underset{|}{\mathrm{C}}{=}\underset{|}{\mathrm{C}}{-} \longrightarrow {-}\underset{|}{\overset{\overset{\mathrm{R}}{|}}{\mathrm{C}}}{-}\underset{|}{\dot{\mathrm{C}}}{-}$$

---

[1] For books on free-radical mechanisms, see Pryor, "Free Radicals," McGraw-Hill Book Company, New York, 1965; and Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, 1957.

[2] Another type of termination is disproportionation (see p. 157).

[3] For a review of termination reactions, see Lapporte, *Angew. Chem.* **72,** 759–766 (1960).

in which case it must be another free radical; or it may consist of two particles, e.g.,

$$R\cdot + R'H \longrightarrow RH + R'\cdot$$

in which case one must be a molecule and one a free radical, but in any case *a new radical is generated.* This type of step is called *propagation,* since the newly formed radical may now react with another molecule and produce another radical, and so on, until two radicals do meet each other and terminate the process. The process just described is called a *chain reaction,* and there may be hundreds or thousands of propagation steps between an initiation and a termination. Two other types of propagation reactions do not involve a molecule at all. These are (1) cleavage of a radical into, necessarily, a radical and a molecule and (2) rearrangement of one radical to another (see Chapter 18). When free radicals are highly reactive (for example, alkyl radicals), chains are long, since reactions occur with many molecules; but with radicals of low reactivity (for example, aryl radicals), the radical may be unable to react with anything until it meets another radical, so that chains are short, or the reaction may be a nonchain process. In any particular chain process there is usually a wide variety of propagation and termination steps. Because of this, these reactions lead to many products and are often difficult to treat kinetically.

The following are some general characteristics of free-radical reactions:

1. Reactions are fairly similar whether they are occurring in the vapor or liquid phase.
2. They are largely unaffected by the presence of acids or bases or by changes in the polarity of solvents, except that nonpolar solvents may suppress competing ionic reactions.
3. They are initiated or accelerated by typical free-radical sources, such as the peroxides referred to, or by light. In the latter case there arises the concept of *quantum yield.* The quantum yield is the efficiency of the reaction: how many molecules of product are formed per quantum absorbed. This may be quite high (e.g., 1000%) if each quantum generates a long chain, or low, in the case of nonchain processes.
4. Their rates are decreased, or the reactions are suppressed entirely, by substances which scavenge free radicals, e.g., nitric oxide, molecular oxygen, or benzoquinone. These substances are called *inhibitors.*

Some mechanisms which involve free-radical intermediates also display ionic characteristics.

In this chapter are discussed free-radical substitution reactions. Free-radical additions to unsaturated compounds and rearrangements are discussed in Chapters 15 and 18, respectively. In addition, many of the oxidation-reduction reactions considered in Chapter 19 involve free-radical mechanisms. Several important types of free-radical reactions do not usually lead to reasonable yields of pure products and are not generally treated in this book. Among these are polymerizations and high-temperature pyrolyses.

Free-radical Substitution Mechanisms. In a free-radical substitution reaction

$$\mathrm{R{-}X} \longrightarrow \mathrm{R{-}Y} \tag{1}$$

there must first be a cleavage of the substrate RX so that R· radicals are produced. This may happen by a spontaneous cleavage

$$\mathrm{R{-}X} \longrightarrow \mathrm{R\cdot} + \mathrm{X\cdot} \tag{2}$$

it may be caused by light or heat, or, more often, there is no actual cleavage, but R· is produced by an *abstraction:*

$$\mathrm{R{-}X} + \mathrm{W\cdot} \longrightarrow \mathrm{R\cdot} + \mathrm{W{-}X} \tag{3}$$

W· is produced by adding a compound, such as a peroxide, which spontaneously forms free radicals. Such a compound is called an *initiator.* Once R· is formed, it may go to product in two ways, by abstraction

$$\mathrm{R\cdot} + \mathrm{Y{-}Z} \longrightarrow \mathrm{R{-}Y} + \mathrm{Z\cdot} \tag{4}$$

or by coupling with another radical

$$\mathrm{R\cdot} + \mathrm{Y\cdot} \longrightarrow \mathrm{R{-}Y} \tag{5}$$

Cleavage steps like (2) have been called S_H1 (H for homolytic), and abstraction steps like (3) and (4) have been called S_H2; and it has been proposed that reactions be classified as S_H1 or S_H2 on the basis of whether RX is converted to R by (2) or (3),[4] but this terminology has not often been adopted.

It would be interesting to know just how abstraction steps like (3) [and for that matter (4)] occur. Does the radical make a frontside attack, as in S_E2 reactions or a backside attack as in S_N2 reactions? The details of these steps are not known, despite much work.[5] Stereochemical studies are not easy to make, since radicals do not retain configuration.

Mechanisms at an Aromatic Substrate.[6] When the R in reaction (1) is aromatic, then the simple abstraction mechanism just discussed may be operating, especially in gas-phase reactions. However, mechanisms of this type cannot account for all reactions of aromatic substrates. In processes such as the following (see reactions **4-15** and **4-17**):

$$\mathrm{Ar\cdot} + \mathrm{ArH} \longrightarrow \mathrm{Ar{-}Ar} \tag{6}$$

---

[4] Eliel, in Newman, "Steric Effects in Organic Chemistry," pp. 142–143, John Wiley & Sons, Inc., New York, 1956.

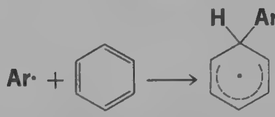
[5] Pryor and Pickering, *J. Am. Chem. Soc.* **84,** 2705 (1962). For a discussion of the transition state of radical-abstraction steps, see Szwarc, in "The Transition State," *Chem. Soc.* (*London*) *Spec. Publ.* **16,** 91–117 (1962).

[6] For a treatise, see Williams, "Homolytic Aromatic Substitution," Pergamon Press, New York, 1960.

which occur in solution, the coupling of two rings cannot be explained on the basis of a simple abstraction

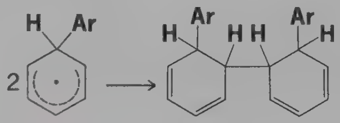
$$\mathrm{Ar\cdot} + \mathrm{ArH} \longrightarrow \mathrm{Ar{-}Ar} + \mathrm{H\cdot} \qquad (7)$$

since, as discussed on page 526, abstraction of an entire group such as phenyl by a free radical is very unlikely. The products may be explained by a mechanism similar to that of electrophilic and nucleophilic aromatic substitution. In the first step, the radical attacks the ring in much the same way as would an electrophile or a nucleophile:



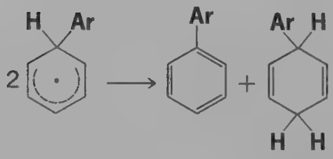
(8)

The intermediate is relatively stable because of the resonance. The reaction may terminate in three ways: by simple coupling, or by disproportionation



(9)

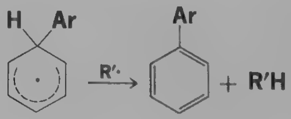
1



(10)

2

or, if a species (R′·) is present which abstracts hydrogen, by abstraction



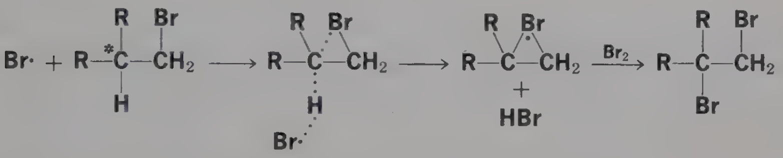
(11)

1 is a partially hydrogenated quarterphenyl. Of course, the coupling need not be ortho-ortho, and other isomers may also be formed. Among the evidence for steps (9) and (10) was isolation of compounds of types **1** and **2**,[7] although normally under the reaction conditions dihydrobiphenyls like **2** are oxidized to the corresponding biphenyls. Other evidence is the absence of isotope effects, which would be expected if the rate-determining step were (7), which involves cleavage of the Ar—H bond. In the mechanism just

[7] De Tar and Long, *J. Am. Chem. Soc.* **80**, 4742 (1958).

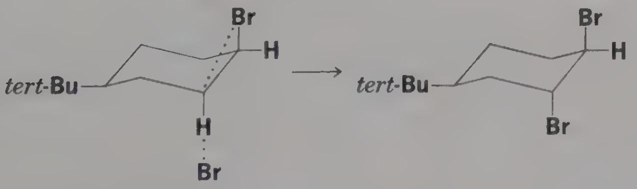
given, the rate-determining step (8) does not involve loss of hydrogen. A similar mechanism has been shown where the attacking radical was HO· or HO_2· (reaction **4-5**).

Neighboring-group Assistance in Free-radical Reactions. In a few cases it has been shown that cleavage steps (2) and abstraction steps (3) have been accelerated by the presence of neighboring groups. Photolytic halogenation (reaction **4-1**) is a process which normally leads to mixtures of many products. However, bromination of carbon chains containing a halogen atom occurs with high specificity. Bromination of alkyl bromides gave 84 to 94% substitution at the carbon adjacent to the halogen already in the molecule.[8] This unusual result has been explained by a mechanism in which abstraction (2) is assisted by a neighboring halogen atom:[9]



(12)

In the normal mechanism, Br· abstracts a hydrogen from RH, leaving R·. When a bromine is present in the proper position, it assists this process, giving a cyclic intermediate. In the final step (very similar to R· + $Br_2 \longrightarrow$ RBr + Br·) the ring is broken. If this mechanism is correct, the configuration at the substituted carbon (marked *) should be retained. This has been shown to be the case.[9] Additional evidence for this mechanism was shown in bromination of *cis*-4-bromo-*tert*-butylcyclohexane. In this compound the bromo group is forced to be axial, by the presence of the *tert*-butyl group (see p. 108). Substitution occurred in the 3-position and was trans, as would be expected by the neighboring-group mechanism:[10]



(13)

The trans isomer, in which the bromine is equatorial and therefore in a much poorer position to be a neighboring group, was both less reactive and less selective than the cis. Low reactivity is normally associated with high selectivity, but, in this case, neighboring bromine (in the cis isomer) both accelerates the reaction and makes the attack specific, both as to position and to steric direction. A similar type of intermediate has been shown, when a bromo group was in the proper position, in the Hunsdiecker reaction[11] (**4-26**). Neighboring-group participation in cleavage reactions (2) has also been shown, in the case of decomposition of *tert*-butyl peresters.[12] The neighboring group in this case was SR.

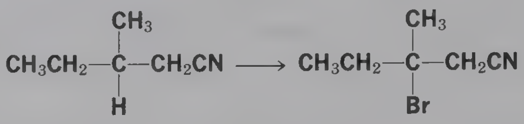
---

[8] Thaler, *J. Am. Chem. Soc.* **85,** 2607 (1963).

[9] Skell, Tuleen, and Readio, *J. Am. Chem. Soc.* **85,** 2849 (1963). Also see Cava, Krieger, Pohlke, and Mangold, *J. Am. Chem. Soc.* **88,** 2615 (1966).

[10] Skell and Readio, *J. Am. Chem. Soc.* **86,** 3334 (1964).

The above facts support the neighboring-group mechanism for certain free-radical substitutions. However, Haag and Heiba have shown[13] that photobromination of optically active 1-cyano-2-methylbutane proceeded with high positional selectivity, to give 1-cyano-2-bromo-2-methylbutane, with predominant retention of configuration:

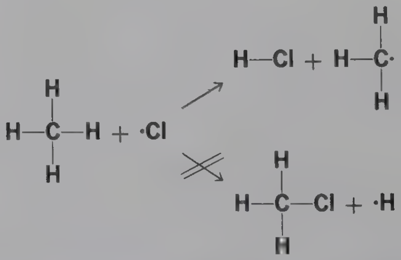


$$CH_3CH_2-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-CH_2CN \longrightarrow CH_3CH_2-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle Br}{|}}{C}}-CH_2CN$$

Since CN is not likely to act as a neighboring group, this result casts doubt on the explanation offered for the parallel case of 1-bromo compounds. Retention of configuration was explained by the normal substitution process, with the product-forming step occurring very rapidly, before the free radical could racemize.

REACTIVITY

Reactivity for Aliphatic Substrates. In a chain reaction, the step that determines what the product will be is most often an abstraction step. What is abstracted by a free radical is almost never a tetra- or trivalent atom, and not often a divalent one. Nearly always it is univalent, and so, for organic compounds, it is hydrogen or halogen. For example, a reaction between a chlorine atom and methane gives a methyl radical and not a hydrogen atom:



Most studies of aliphatic reactivity have been made with hydrogen as the leaving group and chlorine atoms as the abstracting species. In these reactions, every hydrogen in the substrate is a potential leaving group, and mixtures are usually obtained. However, the abstracting radical is not

---

[11] Applequist and Werner, *J. Org. Chem.* **28,** 48 (1963).

[12] Bentrude and Martin, *J. Am. Chem. Soc.* **84,** 1561 (1963); Tuleen, Bentrude, and Martin, *J. Am. Chem. Soc.* **85,** 1938 (1963); Fisher and Martin, *J. Am. Chem. Soc.* **88,** 3382 (1966).

[13] Haag and Heiba, *Tetrahedron Letters* **1965,** 3679.

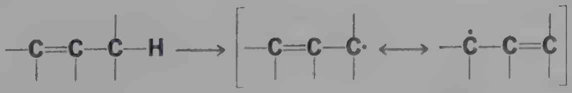
TABLE 1. Relative susceptibility to attack by Cl· of primary, secondary, and tertiary positions at 100 and 600°, in the gas phase[14]

	Primary	*Secondary*	*Tertiary*
100°	1	4.3	7.0
600°	1	2.1	2.6

totally unselective, and some positions on a molecule lose hydrogen more easily than others. We may discuss the position of attack under several headings.[15]

1. *Alkanes.* The tertiary hydrogens of an alkane are the ones that are preferentially abstracted by any radical, with secondary hydrogens being next preferred. This is in the same order as **D** values (see p. 25) for these types of C—H bonds (Table 1 in Chapter 5, p. 155), although this agreement is partly fortuitous, since **D** values are not always in agreement with position of abstraction.[16] The extent of the preference depends upon the reactivity (hence selectivity) of the abstracting radical and upon the temperature. Table 1 shows that at high temperatures selectivity decreases, as might be expected. An example of the effect of radical reactivity may be noted in a comparison of the selectivity of fluorine atoms with that of bromine atoms. For the former, the ratio of primary to tertiary abstraction (of hydrogen) is 1:1.4, while for the less reactive bromine atom this ratio is 1:1600.[15] Among secondary positions, the most susceptible is usually that one next to the end of the chain,[17] though the differences are small.

2. *Olefins.* When the substrate molecule contains a double bond, then treatment with chlorine or bromine usually leads to addition rather than substitution. However, for other free radicals (and even for chlorine or bromine atoms, when they do abstract a hydrogen) the position of attack is perfectly clear. Vinylic hydrogens are practically never abstracted, and allylic hydrogens are greatly preferred to other positions of the molecule. This is hardly surprising, since the resulting allylic radicals are stabilized by resonance:



Also unsurprising is the fact that allylic rearrangements (see p. 270) are common in these cases.[18] The preference for allylic abstraction has been shown for chlorination, by carrying out the reaction at 600°. At this temperature addition to the double bond is reversed, and the allylic hydrogen is preferentially abstracted.

---

[14] Hass, McBee, and Weber, *Ind. Eng. Chem.* **28,** 333 (1936).

[15] For reviews, see Davidson, *Quart. Rev. (London)* **21,** 249–258 (1967); Trotman-Dickenson, *Advan. Free Radical Chem.* **1,** 1–38 (1965); and Tedder, *Quart. Rev. (London)* **14,** 336–356 (1960).

[16] Russell and Brown, *J. Am. Chem. Soc.* **77,** 4578 (1955).

[17] Smit and Den Hertog, *Rec. trav. chim.* **83,** 891 (1964).

[18] For a review, see Walling, in Mayo, "Molecular Rearrangements," pp. 407–455, Interscience Publishers, Inc., New York, 1963, pp. 431–438.

3. *Alkyl side chains of aromatic rings.* The preferential position of attack on a side chain is usually the one α to the ring. For both active radicals such as chlorine and phenyl, and less active ones like bromine, such attack is faster than that at a primary carbon, but for the active radicals, benzylic attack is slower than for tertiary positions, while for the inactive ones, it is faster. Two or three aryl groups on a carbon activate its hydrogens even more, as would be expected from the resonance involved. These statements may be illustrated by the following abstraction ratios:[19]

	Me—H	$MeCH_2$—H	Me_2CH—H	Me_3C—H	$PhCH_2$—H	Ph_2CH—H	Ph_3C—H
Br	0.0007	1	220	19,400	64,000	6.2×10^5	1.14×10^6
Cl	0.004	1	4.3	6.0	1.3	2.6	9.5

However, many anomalous results have been reported for these substrates. The benzylic position is not always the most favored. One thing which is certain is that *aromatic* hydrogens are seldom abstracted if there are aliphatic ones to compete.

4. *Compounds containing electron-withdrawing substituents.* Electron-withdrawing groups greatly deactivate adjacent positions. Compounds of the type Z—CH_2—CH_3 are attacked predominantly or exclusively at the β position, when Z is COOH, COCl, CN, COOR, SO_2Cl, or CX_3. Such compounds as acetic acid and acetyl chloride are not attacked at all. For halogenations this is in sharp contrast to electrophilic halogenations (reactions **2-4**, p. 458, and **2-5**, p. 460), where *only* the α position is substituted. This deactivation of α positions is also at variance with the expected stability of the resulting radicals, since they would be expected to be stabilized by resonance similar to that for allylic and benzylic radicals. The explanation seems to be that a purely inductive effect is operating. The chlorine atom is an *electrophilic* radical and looks for positions of high electron density. Positions next to electron-withdrawing groups have low electron densities and are therefore shunned. There are other facts in accord with this explanation. Not all radicals are electrophilic. The methyl radical is nucleophilic, and its behavior is opposite; for example, relative rates of abstraction at the α and β carbons of propionic acid are:[15]

	CH_3—	CH_2—COOH
Me·	1	7.8
Cl·	1	0.03

For longer chains the inductive effect continues, and the β position is also deactivated, though much less so than the α position (however, there are contrary reports in the literature).[20] When Z is a halogen, simple generalizations cannot be made. In some cases, the expected inductive effect seems to be operating, and in others the neighboring-group effect (p. 525) gives mainly β substitution, but, in still other cases, results are obtained which defy simple explanations. For example, these are the relative abstraction ratios for some simple alkyl halides:[20,21]

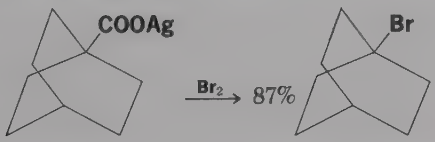
---

[19] Russell and DeBoer, *J. Am. Chem. Soc.* **85**, 3136 (1963).

C—C—Cl	C—C—C—Cl	C—C—C—C—Cl
20 80	40 60 0	13 49 28 10

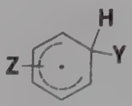
Abstraction of a halogen has been studied much less, but it has been shown[22] that the rates are extremely sensitive to the nature of the halide. The stable free radical 1-ethylcarbomethoxypyridyl abstracted chlorine from carbon tetrachloride about 10^8 times more rapidly than from dichloromethane. In abstractions by aryl radicals, bromine is abstracted more readily, and chlorine less readily, than hydrogen.[23]

Reactivity at a Bridgehead. Many free-radical reactions have been observed to occur at bridgehead carbons,[24] for example (see reaction **4-26**):[25]



demonstrating that the free radical need not be planar. However, treatment of norbornane with sulfuryl chloride and benzoyl peroxide gave mostly 2-chloronorbornane, although the bridgehead position is tertiary.[26] So, while bridgehead free-radical substitution is possible, it is not preferred.

Reactivity in Aromatic Substrates. Free-radical substitution at an aromatic carbon seldom takes place by a mechanism in which a hydrogen is abstracted to give an aryl radical. Reactivity considerations here are similar to those in Chapters 11 and 12; that is, we need to know which position on the ring will be attacked to give the intermediate



---

[20] Singh and Tedder, *J. Chem. Soc.* **1964**, 4737.
[21] Walling, Ref. 1, pp. 362–364.
[22] Kosower and Schwager, *J. Am. Chem. Soc.* **86**, 5528 (1964).
[23] Cadogan, Hey, and Hibbert, *J. Chem. Soc.* **1965**, 3939, 3950.
[24] For a review, see Schöllkopf, *Angew. Chem.* **72**, 147–159 (1960).
[25] Grob, Ohta, Renk, and Weiss, *Helv. Chim. Acta* **41**, 1191 (1958).
[26] Roberts, Urbanek, and Armstrong, *J. Am. Chem. Soc.* **71**, 3049 (1949).

The obvious way to obtain this information is to carry out reactions with various Z groups and to analyze the products for percent ortho, meta, and para isomers, as is so often done for electrophilic substitution. However, this procedure is much less accurate in the case of free-radical substitutions because of the many side reactions. It may be, for example, that in a given case the ortho position is more reactive than the para, but the intermediate from the para attack may go on to product, while that from ortho attack gives a side reaction. In such a case, analysis of the three products will not give a true picture of which position was most susceptible to attack. The following generalizations may nevertheless be drawn, although there has been much controversy over just how meaningful such conclusions are:[27]

1. All substituents increase reactivity at ortho and para positions over that of benzene. There is no great difference between electron-donating and -withdrawing groups.
2. Reactivity at meta positions is usually similar to that of benzene, perhaps slightly higher or lower.
3. Reactivity at ortho positions is usually somewhat greater than at para positions, except where a large group decreases ortho reactivity for steric reasons.
4. Substituents have much less effect than in electrophilic or nucleophilic substitution; hence the partial rate factors (see p. 391) are not great. Partial rate factors for a few groups are given in Table 2.[28]

It should be remembered that in *alternant hydrocarbons,* the position of attack is the same for electrophilic, nucleophilic, and free-radical substitution (see p. 391).

---

[27] De Tar, *J. Am. Chem. Soc.* **83,** 1014 (1961) (book review); Dickerman and Vermont, *J. Am. Chem. Soc.* **84,** 4150 (1962); Morrison, Cazes, Samkoff, and Howe, *J. Am. Chem. Soc.* **84,** 4152 (1962).

[28] Hey, Orman, and Williams, *J. Chem. Soc.* **1961,** 565. The value for COOMe is from Hey, Saunders, and Williams, *J. Chem. Soc.* **1964,** 3409. These values are for phenyl as the attacking radical. Values for other aryl radicals have been reported by Migita, Morikawa, and Simamura, *Bull. Chem. Soc. Japan* **36,** 980 (1963); Ito, Migita, Morikawa, Ōkuni, and Simamura, *Bull. Chem. Soc. Japan* **36,** 985 (1963); Ito, Migita, Morikawa, and Simamura, *Bull. Chem. Soc. Japan* **36,** 992 (1963). These workers also reported values for the phenyl radical which differed in magnitude, but not in tendency, from those of Hey et al.

TABLE 2. Partial rate factors for attack of substituted benzenes by phenyl radicals[28]

Z	*Partial rate factor*		
	o	*m*	*p*
H	1	1	1
NO_2	5.5	0.86	4.9
Cl	1.6	1.0	1.2
CH_3	2.5	0.71	1.0
CMe_3	0.46	0.94	1.0
COOMe	3.04	0.93	2.72

TABLE 3. Some common free radicals in decreasing order of activity
The E values represent activation energies for the reaction $X\cdot + C_2H_6 \longrightarrow X{-}H + C_2H_5\cdot$.[15] RO· is more active than R· but less active than Cl·.[29] *iso*-Pr· is less active than Me·, and *tert*-Bu· still less so[30]

Radical	*E(kcal/mole)*
F·	0.2
Cl·	1.0
$CF_3\cdot$	7.5
H·	8.7
$CH_3\cdot$	11.2
Br·	13.3

Reactivity in the Attacking Radical. We have already seen that less active radicals are much more selective than active radicals (p. 527). The bromine atom is so selective that, when only primary hydrogens are available, as in neopentane or *tert*-butylbenzene, the reaction is slow or nonexistent; and isobutane can be selectively brominated to give *tert*-butyl bromide in high yields. However, toluene reacts with bromine atoms instantly. The dissociation energy (**D**) of the C—H bond is more important for radicals of low reactivity than for highly reactive radicals, since bond breaking in the transition state is greater. Thus, bromine shows a greater tendency than chlorine to attack α to an electron-withdrawing group because the energy of the C—H bond there is lower than in other places in the molecule.

Some free radicals (e.g., triphenylmethyl) are so unreactive that they do not abstract hydrogens at all. Table 3 lists some common free radicals in approximate order of reactivity.[15]

It has been mentioned that some free radicals (e.g., chloro) are electrophilic and some (e.g., methyl) are nucleophilic. It must be borne in mind that these tendencies are relatively slight compared to the electrophilicity of a positive ion or the nucleophilicity of a negative ion. The predominant character of a free radical is neutral, whether it has slight electrophilic or nucleophilic tendencies.

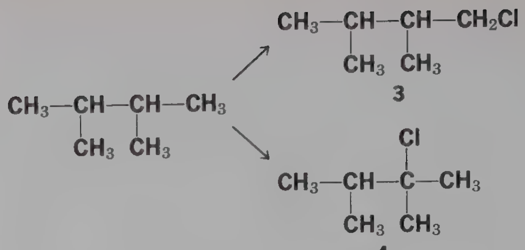
The Effect of Solvent on Reactivity. As has been noted earlier, the solvent usually has little effect on free-radical substitutions, in contrast to ionic ones: indeed, reactions in solution are often quite similar in character to those in the gas phase, where there is no solvent at all. However, in certain cases the solvent *can* make an appreciable difference. The chlorination of 2,3-dimethylbutane in aliphatic solvents gave about 60% **3** and 40% **4**, while in aromatic solvents the ratio became about 10:90:[31]

---

[29] Bogomol'nyi, Erusalimskii, and Pokrovskii, *J. Gen. Chem. USSR* **31**, 2497 (1961); Shaw and Trotman-Dickenson, *Proc. Chem. Soc.* **1959**, 61.

[30] Kharasch, Hambling, and Rudy, *J. Org. Chem.* **24**, 303 (1959).

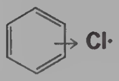
[31] Russell, *J. Am. Chem. Soc.* **80**, 4987, 4997, 5002 (1958), *J. Org. Chem.* **24**, 300 (1959).



3

4

This result is attributed to complex formation between the aromatic solvent and the chlorine atom



which makes the chlorine less reactive and more selective. This type of effect is not found in cases where the differences in abstractability are caused by inductive effects of electron-withdrawing groups (p. 528). In such cases aromatic solvents make no difference.[32] Differences caused by solvents have also been reported in reactions of *tert*-butoxy radicals.[33] Some of the anomalous results obtained in the chlorination of aromatic side chains (p. 528) may also be explained by this type of complexing, in this case not with the solvent, but with the reacting species.[34]

REACTIONS

The reactions in this chapter are classified according to leaving group. The most common leaving groups are hydrogen and nitrogen (from the diazonium ion), and these are considered first.[35]

Hydrogen as Leaving Group

A. Substitution by halogen

4-1 Halogenation at an alkyl carbon[36]

$$\mathrm{R{-}H} + \mathrm{Cl_2} \xrightarrow{h\nu} \mathrm{R{-}Cl}$$

Alkanes may be chlorinated or brominated by treatment with chlorine or bromine in the presence of visible or ultraviolet light. The reaction also may be applied to alkyl chains containing many functional groups. The reaction is usually not useful for preparative purposes precisely because it is so general: not only does substitution take place at virtually every alkyl carbon in the molecule, but di- and polyhalogen substitution almost invariably occurs also, even if there is a large molar ratio of substrate to halogen. Thus methane always gives chloro-, dichloro-, trichloro-, and tetrachloromethane, in ratios which differ depending on the initial molar ratio of methane to chlorine, but all four products are always obtained. When functional groups are present, then the principles are those outlined on page 528; favored positions are those α to aromatic rings, while positions α to electron-withdrawing groups are least likely to be substituted. Tertiary carbons are most likely to be attacked, and primary least. Positions α to an OR group are very readily attacked. Nevertheless, mixtures are nearly always obtained. This may be contrasted to the specificity of electrophilic halogenation (reactions **2-4**, p. 458, and **2-5**, p. 460), which always takes place α to a carbonyl group. Of course, if a *mixture* of halides is what is desired, then the reaction is usually quite satisfactory, and indeed it is of considerable industrial importance. For obtaining pure compounds the most commonly used substrates are those which have methyl groups on aromatic rings, since few cases are known where halogen atoms substitute at an aromatic position.[37] Of course, ring substitution *does* take place in the presence of a positive-ion-forming catalyst (reaction **1-11**, p. 403). In addition to mixtures of various alkyl halides, traces of other products are obtained. These include hydrogen gas, olefins, higher alkanes, lower alkanes, and halogen derivatives of *them*.

---

[32] Russell, *Tetrahedron* **8**, 101 (1960).

[33] Walling and Wagner, *J. Am. Chem. Soc.* **85**, 2333 (1963).

[34] Russell, Ito, and Hendry, *J. Am. Chem. Soc.* **85**, 2976 (1963).

[35] For a review of *intramolecular* free-radical substitutions, see Heusler and Kalvoda, *Angew. Chem. Intern. Ed. Engl.* **3**, 525–538 (1964). For a review of free-radical ring-closure reactions, see Julia, *Record Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) **25**, 3–29 (1964).

[36] For a review, see Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," pp. 282–331, 355–382, 387–401, The Macmillan Company, New York, 1964.

Since the bromine atom is less reactive than the chlorine atom, it would be expected that greater specificity would be obtained in brominations, and this is true. As indicated on page 531, it is often possible to brominate tertiary positions selectively.[38] High specificity may also be obtained where the neighboring-group mechanism (p. 525) can operate.

As already mentioned, halogenation may be performed with chlorine or bromine. Fluorine has also been used,[39] but seldom, because it is too reactive and hard to control. It often breaks carbon chains down into smaller units, a side reaction which sometimes becomes troublesome in chlorinations too. Iodine can be used, if the activating light has a wavelength of 1849 Å,[40] but iodinations are seldom attempted, largely because the HI formed reduces the alkyl iodide. Many other halogenation agents have been employed, the most common of which is sulfuryl chloride, SO_2Cl_2. The reaction in this case is more rapid and convenient than the one with chlorine itself. Other agents used have been N-bromosuccinimide (see reaction **4-2**), CCl_4, oxalyl chloride, $BrCCl_3$,[41] PCl_5,[42] phosgene, *tert*-butyl hypobromite[43] and hypochlorite[44] (see also reaction **4-28**), and trichloromethanesulfonyl chloride and bromide.[45] In all of these cases a chain-initiating catalyst is required, usually peroxides or ultraviolet light.

---

[37] Dermer and Edmison, *Chem. Rev.* **57**, 77–122 (1957), pp. 110–112. An example of free-radical ring halogenation may be found in Engelsma and Kooyman, *Rec. trav. chim.* **80**, 526, 537 (1961). For a review of aromatic halogenation in the gas phase, see Kooyman, *Advan. Free Radical Chem.* **1**, 137–153 (1965).

[38] For example, see Siegmann, Beers, and Huisman, *Rec. trav. chim.* **83**, 67 (1964).

[39] Henne, *Org. Reactions* **2**, 49–93 (1944), pp. 69–73.

[40] Gover and Willard, *J. Am. Chem. Soc.* **82**, 3816 (1960).

[41] Huyser, *J. Am. Chem. Soc.* **82**, 391 (1960).

[42] Wyman, Wang, and Freeman, *J. Org. Chem.* **28**, 3173 (1963).

[43] Walling and Padwa, *J. Org. Chem.* **27**, 2976 (1962).

In all cases, the mechanism involves a free-radical chain:[46]

Initiation $$X_2 \xrightarrow{h\nu} 2X\cdot$$

Propagation $$RH + X\cdot \longrightarrow R\cdot + XH$$
$$R\cdot + X_2 \longrightarrow RX + X\cdot$$

Termination $$R\cdot + X\cdot \longrightarrow RX$$

When the reagent is halogen, initiation occurs as shown above. When it is another reagent, a similar cleavage occurs, catalyzed by light or, more commonly, peroxides. In the latter case *both* of the free radicals produced (for example, Cl· and *tert*-BuO· from *tert*-BuOCl) may now abstract hydrogens. The two propagation steps shown are those which lead directly to the principal products (RX and HX), but many other propagation steps are possible, and many occur. Similarly, the only termination step shown is the one that leads to RX, but any two radicals may combine. Thus, products like hydrogen, higher alkanes, and alkyl halides may be accounted for by steps like these (these are for chlorination of methane, but analogous steps may be written for other substrates):

$$\begin{aligned}
Cl\cdot + HCl &\longrightarrow Cl{-}Cl + H\cdot \\
H\cdot + H\cdot &\longrightarrow H{-}H \\
CH_3\cdot + CH_3\cdot &\longrightarrow CH_3CH_3 \\
CH_3CH_3 + Cl\cdot &\longrightarrow CH_3CH_2\cdot + HCl \\
CH_3CH_2\cdot + Cl_2 &\longrightarrow CH_3CH_2Cl + Cl\cdot \\
CH_3CH_2\cdot + CH_3CH_2\cdot &\longrightarrow CH_3CH_3 + CH_2{=}CH_2 \\
CH_3CH_2\cdot + CH_3CH_2\cdot &\longrightarrow CH_3CH_2CH_2CH_3 \\
CH_3CH_2\cdot + HCl &\longrightarrow CH_3CH_3 + Cl\cdot
\end{aligned}$$

etc.

At least when methane is the substrate, the rate-determining step is

$$CH_4 + Cl\cdot \longrightarrow CH_3\cdot + HCl$$

since an isotope effect of 12.1 was observed at 0°.[47]

---

[44] Walling and Jacknow, *J. Am. Chem. Soc.* **82**, 6108, 6113 (1960); Anbar and Ginsburg, *Chem. Rev.* **54**, 925–958 (1954), pp. 933–937.

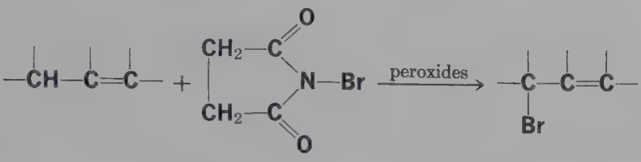
[45] Huyser and Giddings, *J. Org. Chem.* **27**, 3391 (1962); Pinnell, Huyser, and Kleinberg, *J. Org. Chem.* **30**, 38 (1965).

[46] For reviews, see Chiltz, Goldfinger, Huybrechts, Martens, and Verbeke, *Chem. Rev.* **63**, 355–372 (1963); Bratolyubov, *Russ. Chem. Rev.* **30**, 602–612 (1961).

[47] Wiberg and Motell, *Tetrahedron* **19**, 2009 (1963).

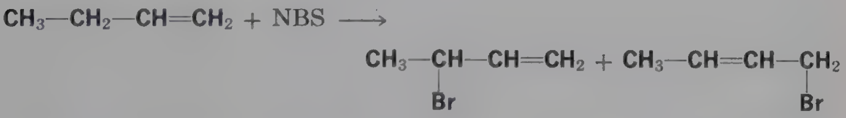
OS **II,** 89, 133, 443, 549; **III,** 737, 788; **IV,** 807, 921, 984; **40,** 54; **42,** 26; **44,** 30; **46,** 81. Also see OS **45,** 86.

4-2 Allylic halogenation



This reaction is actually a special case of reaction **4-1,** but it is important enough to be treated separately.[48] Olefins may be halogenated in the allylic position by a number of reagents, of which N-bromosuccinimide (NBS) is by far the most common. When this reagent is used, the reaction is known as *Wohl-Ziegler bromination.* Other N-bromo amides, including various N-bromohydantoins and N-bromocaprolactam,[49] have also been used, as have N-bromo-*tert*-butylamine[50] and 1,2-dibromo-1,2,3,4-tetrachloroethane[51] (the latter is a *brominating* agent). To a much lesser extent, allylic chlorination has been carried out with N-chlorosuccinimide or *tert*-butyl hypochlorite.[52] With any reagent an initiator is needed, and this is usually a peroxide or, less often, ultraviolet light.

The reaction is usually quite specific at the allylic position, and good yields are obtained. However, when the allylic-radical intermediate is unsymmetrical, then allylic shifts can take place so that mixtures of both possible products are obtained, e.g.,



$$CH_3—CH_2—CH═CH_2 + \text{NBS} \longrightarrow \underset{\displaystyle Br}{CH_3—\underset{|}{CH}}—CH═CH_2 + CH_3—CH═CH—\underset{\displaystyle Br}{\underset{|}{CH_2}}$$

When a double bond has two different α positions (for example, $CH_3—CH═CH—CH_2—CH_3$), then a secondary position is substituted more readily than a primary. The relative reactivity of tertiary hydrogen is not clear, though many substitutions at allylic tertiary positions have been performed.[53] It is possible to brominate both sides of the double bond.[54]

NBS is also a highly specific brominating agent at other positions, including positions α to a carbonyl group, to a C≡C triple bond, and to an aromatic ring (benzylic position). When both a double and a triple bond are in the same molecule, the preferred position is α to the triple bond.[55] Allylic bromination may also be carried out on oximes, in which case it is the tautomeric nitroso form which is brominated:

---

[48] For reviews, see Horner and Winkelmann, in Foerst, "Newer Methods of Preparative Organic Chemistry," vol. 3, pp. 151–198, Academic Press Inc., New York, 1964 [this review also appears in *Angew. Chem.* **71,** 349–365 (1959)]; Djerassi, *Chem. Rev.* **43,** 271–317 (1948); Novikov, Sevost'yanova, and Fainzil'berg, *Russ. Chem. Rev.* **31,** 671–681 (1962), pp. 674–677.

[49] Taub and Hino, *J. Org. Chem.* **25,** 263 (1960).

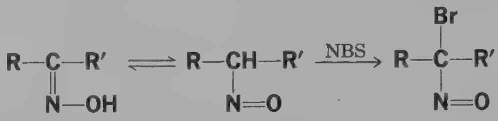
[50] Boozer and Moncrief, *J. Org. Chem.* **27,** 623 (1962).

[51] Huyser and DeMott, *Chem. Ind.* (*London*) **1963,** 1954.

[52] Walling and Thaler, *J. Am. Chem. Soc.* **83,** 3877 (1961).

[53] Dauben and McCoy, *J. Org. Chem.* **24,** 1577 (1959).

[54] Ucciani and Naudet, *Bull. Soc. chim. France* **1962,** 871.

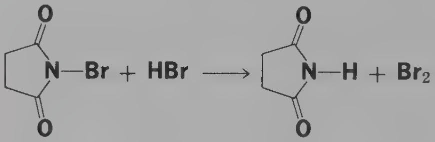


$$\mathrm{R{-}\underset{\underset{\displaystyle N{-}OH}{\|}}{C}{-}R'} \rightleftharpoons \mathrm{R{-}\underset{\underset{\displaystyle N{=}O}{|}}{CH}{-}R'} \xrightarrow{\text{NBS}} \mathrm{R{-}\overset{\overset{\displaystyle Br}{|}}{\underset{\underset{\displaystyle N{=}O}{|}}{C}}{-}R'}$$

That the mechanism of allylic bromination is of the free-radical type was demonstrated by Dauben and McCoy,[56] who showed that the reaction was very sensitive to free-radical initiators and inhibitors and indeed did not proceed at all unless at least a trace of initiator was present. Subsequent work indicated that the species which actually abstracts hydrogen from the substrate is the bromine atom. The reaction is initiated by small amounts of Br·. Once it is formed, the main propagation steps are

1. $\mathrm{Br\cdot + RH \longrightarrow R\cdot + HBr}$
2. $\mathrm{R\cdot + Br_2 \longrightarrow RBr + Br\cdot}$

The source of the Br_2 is a fast ionic reaction between NBS and the HBr liberated in step 1:



The function of the NBS is therefore to provide a source of Br_2, in a low, steady-state concentration, and to use up the HBr liberated in step 1.[57] It was previously believed that the abstracting species was the succinimide radical (**5**), but there is now much evidence that this species is not involved in the reaction and is probably not even formed. The main evidence is that NBS and Br_2 show similar selectivity;[58] that the various N-bromo amides also show similar selectivity, which would not be the case if a different species was abstracting in each case;[59] and that **5** has proved itself to be a much less stable species than was originally thought, since its dimer shows no tendency to dissociate:[60]

---

[55] Peiffer, *Bull. Soc. chim. France* **1963**, 537.

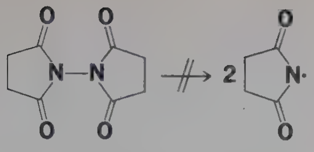
[56] Dauben and McCoy, *J. Am. Chem. Soc.* **81**, 4863 (1959).

[57] This mechanism was originally suggested by Adam, Gosselain, and Goldfinger, *Nature* **171**, 704 (1953), *Bull. Soc. Chim. Belges* **65**, 533 (1956), but did not win acceptance for a number of years.

[58] Walling, Rieger, and Tanner, *J. Am. Chem. Soc.* **85**, 3129 (1963); Russell and Desmond, *J. Am. Chem. Soc.* **85**, 3139 (1963); Russell, DeBoer, and Desmond, *J. Am. Chem. Soc.* **85**, 365 (1963); Pearson and Martin, *J. Am. Chem. Soc.* **85**, 3142 (1963); Skell, Tuleen, and Readio, *J. Am. Chem. Soc.* **85**, 2850 (1963).

[59] Walling and Rieger, *J. Am. Chem. Soc.* **85**, 3134 (1963); Pearson and Martin, Ref. 58.

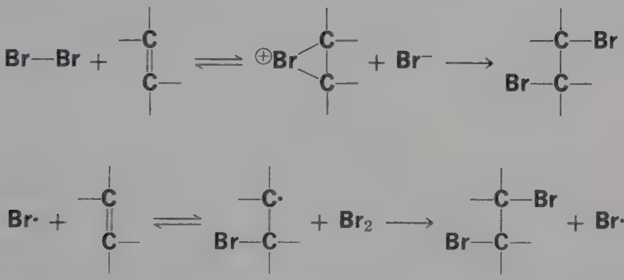
[60] Hedaya, Hinman, Kibler, and Theodoropulos, *J. Am. Chem. Soc.* **86**, 2727 (1964); Koenig and Brewer, *J. Am. Chem. Soc.* **86**, 2728 (1964).



5

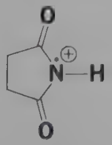
The latter observation casts doubt on the ability of NBS to dissociate.

The question may be asked as to why, if Br_2 is the reacting species, it does not add to the double bond, either by an ionic or by a free-radical mechanism (see reaction **5-22,** p. 610). Apparently the concentration is too low. In bromination of a double bond, only one atom of an attacking bromine molecule becomes attached to the substrate, whether the addition is electrophilic or free radical:



The other bromine comes from another bromine-containing molecule or ion. If the concentration is sufficiently low, there will not be a high probability that the proper species will be in the vicinity once the intermediate forms, and the equilibrium will lie to the left. This slows the rate of addition so that allylic substitution can successfully compete. If this is true, then it should be possible to brominate an olefin in the allylic position without competition from addition, even in the absence of NBS or a similar compound, if a very low concentration of bromine is used and if the HBr is removed as it is formed, so that it is not available to complete the addition step. This has indeed been demonstrated.[61]

In polar solvents, the mechanism may be entirely different, involving electrophilic attack by Br^+. In protonating solvents the protonated radical **6** may be the abstracting species.[62]



6

OS **IV,** 108; **46,** 81.

---

[61] McGrath and Tedder, *Proc. Chem. Soc.* **1961,** 80.

[62] Tanner, *J. Am. Chem. Soc.* **86,** 4674 (1964).

4-3 Halogenation of aldehydes

$$\mathrm{RCHO} + \mathrm{Cl_2} \longrightarrow \mathrm{RCOCl}$$

Aldehydes may be directly converted to acyl chlorides by treatment with chlorine; however, the reaction operates only when the aldehyde does not contain an α hydrogen and even then is not very useful. When there is an α hydrogen, then α halogenation (reaction **2-4**, p. 458) occurs instead. Other sources of chlorine have also been used, among them SO_2Cl_2[63] and *tert*-BuOCl.[64] The mechanisms are probably of the free-radical type.

OS **I**, 155; **44**, 39.

B. Substitution by oxygen

4-4 Hydroxylation at an aliphatic carbon

$$\mathrm{R_3CH} \xrightarrow[\mathrm{HOAc\text{-}H_2SO_4}]{\mathrm{Na_2Cr_2O_7}} \mathrm{R_3COH}$$

Compounds containing susceptible C—H bonds may be oxidized to alcohols. Nearly always, the C—H bond involved is tertiary, so that the product is a tertiary alcohol. This is partly because tertiary C—H bonds are more susceptible to free-radical attack than primary and secondary bonds and partly because the reagents involved would oxidize primary and secondary alcohols further. The reagents may be dichromate and acid;[65] alkaline permanganate;[66] or hydrogen peroxide with nitrates or nitrites.[67] When dichromate is the reagent, the mechanism is probably as follows: a Cr^{6+} species abstracts a hydrogen to give $R_3C\cdot$, which is held in a solvent cage near the resulting Cr^{5+} species. The two species then combine to give R_3COCr^{4+}, which is hydrolyzed to the alcohol. This mechanism predicts retention of configuration; this is largely observed.[68] A similar mechanism has been proposed for the oxidation by permanganate.[69]

OS **IV**, 23.

4-5 Hydroxylation at an aromatic carbon[70]

$$\mathrm{ArH} + \mathrm{H_2O_2} + \mathrm{FeSO_4} \longrightarrow \mathrm{ArOH}$$

---

[63] Arai, *Nippon Kagaku Zasshi* **81**, 1450 (1960) [*CA* **56**, 2370f (1962)], *Bull. Chem. Soc. Japan* **37**, 1280 (1964), **38**, 252 (1965).

[64] Anbar and Ginsburg, *Chem. Rev.* **54**, 925–958 (1954), pp. 937–939.

[65] Sager and Bradley, *J. Am. Chem. Soc.* **78**, 1187 (1956).

[66] Eastman and Quinn, *J. Am. Chem. Soc.* **82**, 4249 (1960).

[67] Inoue, Sonoda, and Tsutsumi, *Bull. Chem. Soc. Japan* **36**, 1549 (1963).

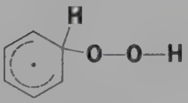
[68] Wiberg and Foster, *J. Am. Chem. Soc.* **83**, 423 (1961), *Chem. Ind.* (*London*) **1961**, 108; Wiberg and Eisenthal, *Tetrahedron* **20**, 1151 (1964).

[69] Wiberg and Fox, *J. Am. Chem. Soc.* **85**, 3487 (1963).

[70] For reviews, see Loudon, *Progr. Org. Chem.* **5**, 47–72 (1961); Dermer and Edmison, *Chem. Rev.* **57**, 77–122 (1957), pp. 101–107; and Williams, "Homolytic Aromatic Substitution," pp. 110–116, Pergamon Press, New York, 1960.

A mixture of hydrogen peroxide and ferrous sulfate, which is called *Fenton's reagent,* may be used to hydroxylate aromatic rings, though yields are usually not high. Another method is x-ray irradiation of a mixture of the aromatic compound with water and cuprous or ferrous salts.[71] Biaryls are usually side products.

Much work has been done on the mechanism of the reaction with Fenton's reagent, and it is known that free aryl radicals (formed by a process such as $HO\cdot + ArH \longrightarrow Ar\cdot + H_2O$) are not intermediates. The mechanism is essentially that outlined on page 524, the only question being whether the attacking species is $HO\cdot$ or $HO_2\cdot$. Evidence for the former has been supplied by Norman and coworkers,[72] but Brodskii and Vysotskaya have shown[73] that hydrogen peroxide labeled in the oxygen gave a phenol which retained 95% of the labeled oxygen. If $HO\cdot$ were formed, it would be expected to exchange rapidly with the solvent water. From this it may be concluded that it is $HO_2\cdot$ which attacks the ring to give **7**, which is then converted to a phenol or a biaryl.

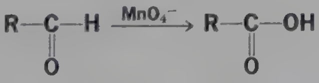


7

Another hydroxylation reaction is the *Elbs reaction.*[74] In this method phenols may be oxidized to *p*-diphenols with $K_2S_2O_8$ in alkaline solution. Anilines usually give ortho substitution. The mechanism is not clear and is probably not of the free-radical type.[75]

See also reactions **1-29** (p. 426) and **3-20** (p. 511).

4-6 Oxidation of aldehydes to acids



$$R-\underset{\underset{O}{\|}}{C}-H \xrightarrow{MnO_4^-} R-\underset{\underset{O}{\|}}{C}-OH$$

Oxidation of aldehydes to carboxylic acids is one of the most common oxidation reactions in organic chemistry and has been carried out with many oxidizing agents, the most popular of which is permanganate in acid, basic, or neutral solution. Acid dichromate and bromine are other reagents frequently employed. Silver oxide is a fairly specific oxidizing agent for aldehydes and does not readily attack other groups. Benedict's and Fehling's solutions oxidize aldehydes, and a test for aldehydes depends on this reaction,

[71] Hotta and Suzuki, *Bull. Chem. Soc. Japan* **36,** 717 (1963); Hotta, Terakawa, Shimada, and Suzuki, *Bull. Chem. Soc. Japan* **36,** 721 (1963); Hotta, Suzuki, and Terakawa, *Bull. Chem. Soc. Japan* **36,** 1255 (1963); Hotta, Suzuki, and Abe, *Bull. Chem. Soc. Japan* **39,** 417 (1966).

[72] Dixon and Norman, *Proc. Chem. Soc.* **1963,** 97; Lindsay-Smith and Norman, *J. Chem. Soc.* **1963,** 2897.

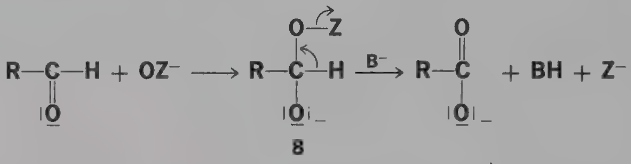
[73] Brodskii and Vysotskaya, *J. Gen. Chem. USSR* **32,** 2241 (1962).

[74] For a review, see Sethna, *Chem. Rev.* **49,** 91–101 (1951).

[75] Behrman, *J. Am. Chem. Soc.* **85,** 3478 (1963).

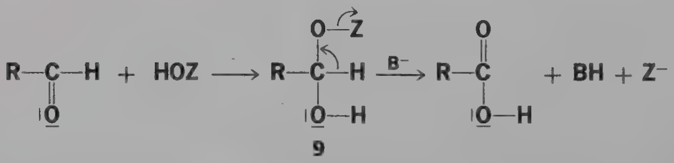
but the method is seldom used for preparative purposes and in any case gives very poor results with aromatic aldehydes. Aldehydes are also oxidized to carboxylic acids by atmospheric oxygen, but the actual direct oxidation product in this case is the peracid RCO_3H, which with another molecule of aldehyde disproportionates to give two molecules of acid (see reaction **4-8**).[76]

Mechanisms of aldehyde oxidation are not firmly established, but there seem to be at least two main types, a free-radical mechanism and an ionic one. In the free-radical process, the aldehydic hydrogen is abstracted to leave an acyl radical, which obtains OH from the oxidizing agent. In the ionic process, the first step is addition of a species OZ^- to the carbonyl bond, to give **8** in alkaline solution and **9** in acid or neutral solution. The aldehydic hydrogen of **8** or **9** is then lost as a proton, to a base, while Z leaves with its electron pair.



$$R{-}\underset{\|}{C}{-}H + OZ^- \longrightarrow R{-}\underset{O^-}{\overset{O-Z}{C}}{-}H \xrightarrow{B^-} R{-}\underset{O^-}{\overset{O}{\overset{\|}{C}}} + BH + Z^-$$

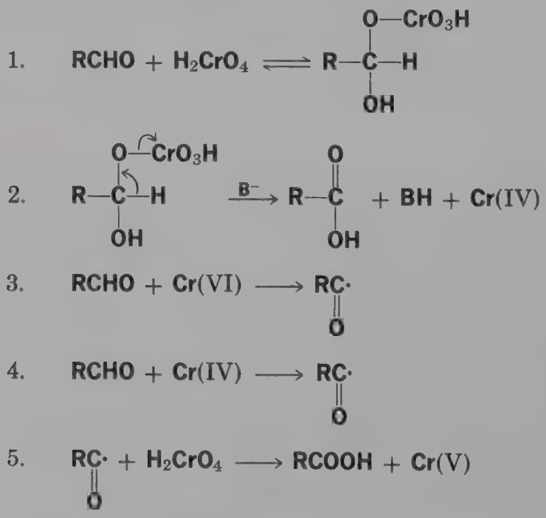
8



$$R{-}\underset{\|}{C}{-}H + HOZ \longrightarrow R{-}\underset{O-H}{\overset{O-Z}{C}}{-}H \xrightarrow{B^-} R{-}\underset{O-H}{\overset{O}{\overset{\|}{C}}} + BH + Z^-$$

9

For oxidations with acid dichromate the picture seems to be quite complex, with several processes of both types going on:[77]



1. $RCHO + H_2CrO_4 \rightleftharpoons R{-}\underset{OH}{\overset{O-CrO_3H}{C}}{-}H$

2. $R{-}\underset{OH}{\overset{O-CrO_3H}{C}}{-}H \xrightarrow{B^-} R{-}\underset{OH}{\overset{O}{\overset{\|}{C}}} + BH + Cr(IV)$

3. $RCHO + Cr(VI) \longrightarrow R\underset{O}{\underset{\|}{C}}\cdot$

4. $RCHO + Cr(IV) \longrightarrow R\underset{O}{\underset{\|}{C}}\cdot$

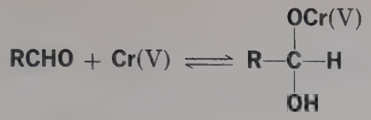
5. $R\underset{O}{\underset{\|}{C}}\cdot + H_2CrO_4 \longrightarrow RCOOH + Cr(V)$

---

[76] For a review of this autoxidation of aldehydes, see McNesby and Heller, *Chem. Rev.* **54**, 325 (1954).

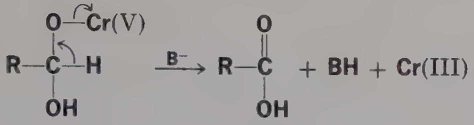
[77] Wiberg and Richardson, *J. Am. Chem. Soc.* **84**, 2800 (1962); Wiberg and Lepse, *J. Am. Chem. Soc.* **86**, 2612 (1964).

6.



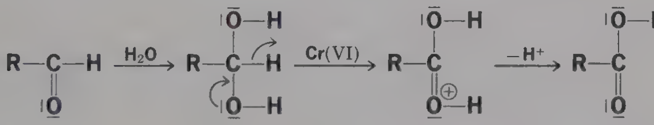
$$\mathrm{RCHO} + \mathrm{Cr(V)} \rightleftharpoons \mathrm{R{-}}\overset{\overset{\displaystyle \mathrm{OCr(V)}}{|}}{\underset{\underset{\displaystyle \mathrm{OH}}{|}}{\mathrm{C}}}\mathrm{{-}H}$$

7.



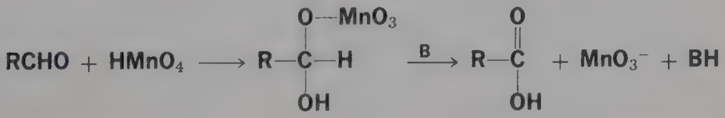
$$\mathrm{R{-}}\overset{\overset{\displaystyle \mathrm{O{-}Cr(V)}}{|}}{\underset{\underset{\displaystyle \mathrm{OH}}{|}}{\mathrm{C}}}\mathrm{{-}H} \xrightarrow{B^-} \mathrm{R{-}}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\underset{\underset{\displaystyle \mathrm{OH}}{|}}{\mathrm{C}}} + \mathrm{BH} + \mathrm{Cr(III)}$$

Steps 1 and 2 represent an oxidation by the ionic pathway by Cr(VI), and steps 6 and 7 a similar oxidation by Cr(V), which is produced in a free-radical process. Either Cr(VI) (step 3) or Cr(IV) (step 4) [Cr(IV) is produced in step 2] may abstract a hydrogen, and the resulting acyl radical is converted to carboxylic acid in step 5. Thus, chromium in three oxidation states is instrumental in oxidizing aldehydes. Still another possible process has been proposed in which the aldehydic hydrogen of a hydrated aldehyde molecule is removed by the dichromate as a *hydride ion:*[78]



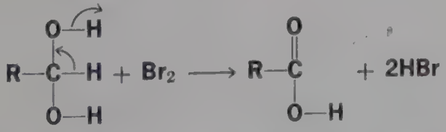
This process is essentially nucleophilic substitution by the tetrahedral mechanism (see p. 274).

The mechanism with permanganate is less well known, but an ionic mechanism has been proposed for neutral and acid permanganate, similar to steps 1 and 2 for dichromate:



$$\mathrm{RCHO} + \mathrm{HMnO_4} \longrightarrow \mathrm{R{-}}\overset{\overset{\displaystyle \mathrm{O{-}MnO_3}}{|}}{\underset{\underset{\displaystyle \mathrm{OH}}{|}}{\mathrm{C}}}\mathrm{{-}H} \xrightarrow{B} \mathrm{R{-}}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\underset{\underset{\displaystyle \mathrm{OH}}{|}}{\mathrm{C}}} + \mathrm{MnO_3^-} + \mathrm{BH}$$

Even less is known about the mechanism with alkaline permanganate. With bromine the mechanism is ionic, the reaction proceeding through the hydrate ($Z = H$). In this case the oxidizing agent (bromine or HOBr) abstracts a hydride ion from the oxygen:[79]



$$\mathrm{R{-}}\overset{\overset{\displaystyle \mathrm{O{-}H}}{|}}{\underset{\underset{\displaystyle \mathrm{O{-}H}}{|}}{\mathrm{C}}}\mathrm{{-}H} + \mathrm{Br_2} \longrightarrow \mathrm{R{-}}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\underset{\underset{\displaystyle \mathrm{O{-}H}}{|}}{\mathrm{C}}} + 2\mathrm{HBr}$$

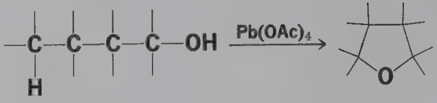
OS **I,** 166; **II,** 302, 315, 538; **III,** 745; **IV,** 302, 493, 499, 919, 972, 974.

---

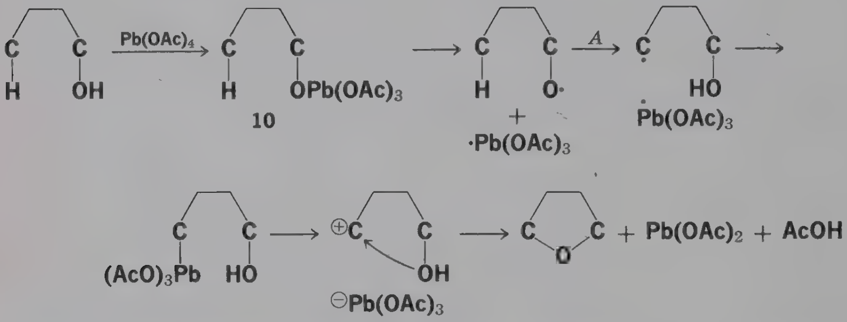
[78] Roček, *Tetrahedron Letters* **1959,** No. 5, 1.

[79] Waters, *Progr. Org. Chem.* **5,** 1–46 (1961); Cullis and Swain, *J. Chem. Soc.* **1962,** 3348; Cox and McTigue, *Australian J. Chem.* **17,** 1210 (1964); Barker and Dahm, *Chem. Commun.* **1965,** 194.

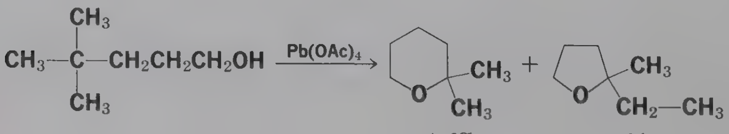
4-7 Formation of cyclic ethers



Alcohols which have a hydrogen in the δ position may be cyclized with lead tetraacetate.[80] Tetrahydrofurans are formed in high yields. Little or no four-membered and six-membered cyclic ethers (oxetanes and tetrahydropyrans, respectively) are obtained even when γ and ε hydrogens are present. The following mechanism is likely:[81]


10

although **10** has never been isolated. The step marked *A* is a 1,5 internal hydrogen abstraction. Such abstractions are well known (see p. 849) and are greatly favored over 1,4 or 1,6 abstractions (the small amounts of tetrahydropyran formed result from 1,6 abstractions). Evidence for the intermediacy of a carbonium ion is that 4,4-dimethylpentanol, which cannot give a normal product, since it has no δ hydrogen, gave 1% of the rearranged product 2-methyl-2-ethyltetrahydrofuran (**11**) in addition to 4 to 6% of the tetrahydropyran:[82]


4–6%

11
1%

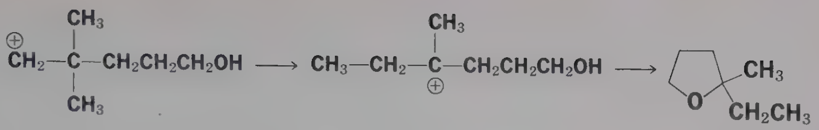
In this case the initial abstraction was 1,6, since a 1,5-abstraction was impossible. **11** was formed by a 1,2-shift of methyl:

---

[80] For a review, see Heusler and Kalvoda, *Angew. Chem. Intern. Ed. Engl.* **3,** 525–538 (1964), pp. 532–534.

[81] Mihailović, Čeković, Maksimović, Jeremić, Lorenc, and Mamuzić, *Tetrahedron* **21,** 2799 (1965).

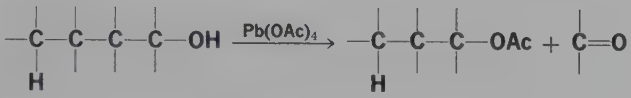
[82] Mihailović, Čeković, and Jeremić, *Tetrahedron* **21,** 2813 (1965).



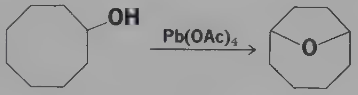
11

Carbonium ions, but not free radicals, commonly rearrange in this manner (see Chapter 18).

Reactions which sometimes compete are oxidation to the aldehyde or acid (reactions **9-3,** p. 862, and **9-20,** p. 883), and fragmentation:



The reaction has been performed intramolecularly:[83]



There are no references in *Organic Syntheses,* but see OS **45,** 57, for a related reaction.

4-8 Formation of hydroperoxides

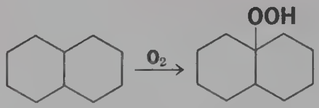
$$RH + O_2 \longrightarrow R{-}O{-}O{-}H$$

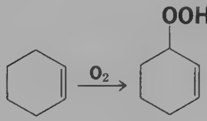
The atmospheric oxidation of a C—H bond to a C—O—O—H group is called *autoxidation.*[84] The reaction occurs when compounds are allowed to stand in air, and is catalyzed by light, so that unwanted autoxidations may be greatly slowed by keeping the compounds in dark places. The hydroperoxides produced often react further, to alcohols, ketones, and more complicated products, so that the reaction is not often used for preparative purposes, although in some cases hydroperoxides have been prepared in good yield. As with other free-radical reactions of C—H bonds, some bonds are attacked more readily than others, and these are the ones we have seen before (pp. 526–529), although the selectivity is very low at high temperatures and in the gas phase. The reaction may be carried out successfully at tertiary (to a lesser extent, secondary), allylic,[85] and benzylic R. The following are actual examples:

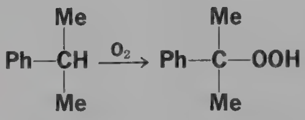
---

[83] Cope, Gordon, Moon, and Park, *J. Am. Chem. Soc.* **87,** 3119 (1965).

[84] The term autoxidation actually applies to any oxidation with atmospheric oxygen. For reviews, see Walling, "Free Radicals in Solution," pp. 397–466, John Wiley & Sons, Inc., New York, 1957; Waters, "Mechanisms of Oxidation of Organic Compounds," pp. 6–16, John Wiley & Sons, Inc., New York, 1964, *Progr. Org. Chem.* **5,** 1–46 (1961), pp. 17–26; Hock and Kropf, *Angew. Chem.* **69,** 313–321 (1957); Twigg, *Chem. Ind. (London)* **1962,** 4–11; and Frank, *Chem. Rev.* **46,** 155–169 (1950).

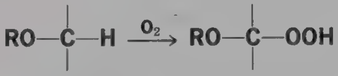






$$\mathrm{Ph{-}\underset{Me}{\overset{Me}{CH}}} \xrightarrow{O_2} \mathrm{Ph{-}\underset{Me}{\overset{Me}{C}}{-}OOH}$$

Another susceptible position is aldehydic C—H, but the peracids so produced are not easily isolated, since they are converted to the corresponding carboxylic acids (reaction **4-6**). The α positions of ethers are also easily attacked by oxygen:



$$\mathrm{RO{-}\underset{|}{\overset{|}{C}}{-}H} \xrightarrow{O_2} \mathrm{RO{-}\underset{|}{\overset{|}{C}}{-}OOH}$$

but the resulting hydroperoxides are almost never isolated. However, this reaction constitutes a hazard in the storage of ethers since solutions of these hydroperoxides and their rearrangement products in ethers are potential spontaneous explosives.

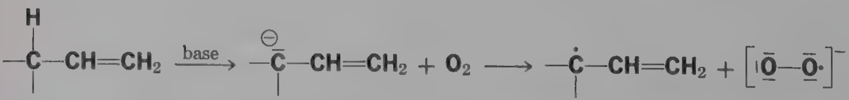
Oxygen itself (a diradical) is too unreactive to be the species which actually abstracts the hydrogen. But if a trace of free radical (say R′·) is produced by some initiating process, then *it* reacts with oxygen to give R′—O—O·, and this type of radical *does* abstract hydrogen, so that the chain is

$$\mathrm{R'OO\cdot} + \mathrm{RH} \longrightarrow \mathrm{R\cdot} + \mathrm{R'OOH}$$

$$\mathrm{R\cdot} + \mathrm{O_2} \longrightarrow \mathrm{R{-}O{-}O\cdot}$$

etc.

In at least some cases (in alkaline media) the radical R· may be produced by formation of a carbanion, and its oxidation (by O_2) to a radical, e.g.,[86]



$$-\underset{|}{\overset{H}{C}}-\mathrm{CH{=}CH_2} \xrightarrow{\text{base}} -\underset{|}{\overset{\ominus}{\bar{C}}}-\mathrm{CH{=}CH_2} + \mathrm{O_2} \longrightarrow -\underset{|}{\overset{\bullet}{C}}-\mathrm{CH{=}CH_2} + \left[\,|\bar{O}-\bar{O}\cdot\,\right]^-$$

---

[85] For a review of the autoxidation of olefins, see Bateman, *Quart. Rev. (London)* **8,** 147–167 (1954).

[86] Barton and Jones, *J. Chem. Soc.* **1965,** 3563.

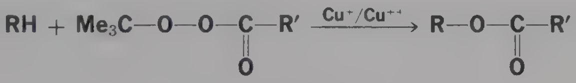
Autoxidations in alkaline media may also proceed by a different mechanism: $R{-}H + \text{base} \longrightarrow R^- + O_2 \longrightarrow ROO^-$.[87]
OS **IV**, 895.

4-9 Formation of peroxides

$$RH + R'OOH \xrightarrow{CuCl} ROOR'$$

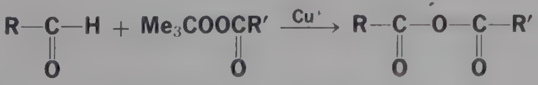
Peroxy groups (ROO) may be introduced into susceptible organic molecules by treatment with a hydroperoxide in the presence of cuprous chloride or other catalysts, for example, cobalt and manganese salts.[88] Very high yields may be obtained. The type of hydrogen replaced is similar to that with N-bromosuccinimide (reaction **4-2**): mainly benzylic, allylic, and tertiary. The mechanism is therefore of the free-radical type, involving ROO· formed from ROOH and the metal ion.

4-10 Acyloxylation and alkyloxylation



$$RH + Me_3C{-}O{-}O{-}\underset{\underset{O}{\|}}{C}{-}R' \xrightarrow{Cu^+/Cu^{++}} R{-}O{-}\underset{\underset{O}{\|}}{C}{-}R'$$

Susceptible positions of organic compounds may be directly acyloxylated by *tert*-butyl peresters, the most frequently used being acetic and benzoic (R′ = Me or Ph).[89] The reaction requires a catalyst (cuprous ion is the actual catalyst, but a trace is all that is necessary, and such traces are usually present in cupric compounds, so that these are often used) and without it is not selective. Acyloxylation has also been achieved with metallic acetates such as lead tetraacetate and mercuric acetate.[90] Similar alkoxylation has been performed with di-*tert*-butyl peroxide.[91] Susceptible positions are similar to those in reaction **4-8:** benzylic, allylic, and the α position of ethers (and sulfides). Terminal olefins are substituted almost entirely in the 3-position—that is, with only a small amount of allylic rearrangement—but internal olefins generally give mixtures containing a large amount of allylic-shift product. If the reaction with olefins is carried out in an excess of another acid, R″COOH, then the ester produced is of *that* acid: ROCOR″. Aldehydes give anhydrides:



$$R{-}\underset{\underset{O}{\|}}{C}{-}H + Me_3COO\underset{\underset{O}{\|}}{C}R' \xrightarrow{Cu^+} R{-}\underset{\underset{O}{\|}}{C}{-}O{-}\underset{\underset{O}{\|}}{C}{-}R'$$

---

[87] Gersmann, Nieuwenhuis, and Bickel, *Tetrahedron Letters* **1963,** 1383.

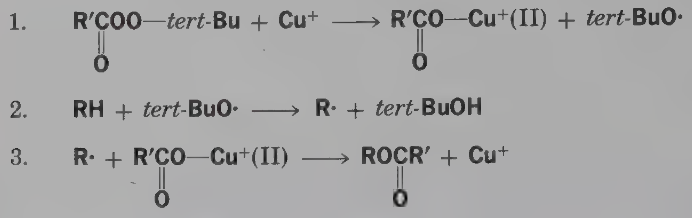
[88] Kharasch and Fono, *J. Org. Chem.* **24,** 72 (1959).

[89] For a review, see Sosnovsky, *Angew. Chem. Intern. Ed. Engl.* **3,** 269–276 (1964).

[90] Anderson and Winstein, *J. Org. Chem.* **28,** 605 (1963); Wiberg and Nielsen, *J. Org. Chem.* **29,** 3353 (1964).

[91] Kharasch and Sosnovsky, *Tetrahedron* **3,** 105 (1958).

Studies of the mechanism of the cuprous-catalyzed reaction show that the most common mechanism is the following:[92]



1. $$R'C(=O)O\text{—}tert\text{-}Bu + Cu^+ \longrightarrow R'C(=O)O\text{—}Cu^+(II) + tert\text{-}BuO\cdot$$

2. $$RH + tert\text{-}BuO\cdot \longrightarrow R\cdot + tert\text{-}BuOH$$

3. $$R\cdot + R'C(=O)O\text{—}Cu^+(II) \longrightarrow ROC(=O)R' + Cu^+$$

12

This mechanism, involving a free radical R·, is compatible with the allylic shifts found.[93] The finding that *tert*-butyl peresters labeled with ^{18}O in the carbonyl oxygen gave ester with 50% of the label in each oxygen[94] is in accord with a combination of R· with the intermediate **12,** in which the copper is ionically bound, so that the oxygens are essentially equivalent. Other evidence is that *tert*-butoxy radicals have been trapped with dienes.[95]

Free-radical acyloxylation of aromatic substrates has been accomplished by heating with cupric benzoate:[96]

$$ArH + 2(PhCOO)_2Cu(II) \longrightarrow ArOCOPh + PhCOOH + 2PhCOOCu(I)$$

OS **III,** 3; **44,** 12.

C. Substitution by sulfur

4-11 Chlorosulfonation

$$RH + SO_2 + Cl_2 \xrightarrow{h\nu} RSO_2Cl$$

The chlorosulfonation of organic molecules with chlorine and sulfur dioxide is called the *Reed reaction.*[97] In scope and in range of products obtained, the reaction is similar to reaction **4-1.** The mechanism is also similar, except that there are two additional main propagation steps:

$$R\cdot + SO_2 \longrightarrow R\text{—}SO_2\cdot$$

$$R\text{—}SO_2\cdot + Cl_2 \longrightarrow R\text{—}SO_2Cl + Cl\cdot$$

---

[92] Kochi, *Tetrahedron* **18,** 483 (1962), *J. Am. Chem. Soc.* **84,** 774 (1962); Kochi and Mains, *J. Org. Chem.* **30,** 1862 (1965).

[93] Goering and Mayer, *J. Am. Chem. Soc.* **86,** 3753 (1964); Denney, Appelbaum, and Denney, *J. Am. Chem. Soc.* **84,** 4969 (1962).

[94] Denney, Denney, and Feig, *Tetrahedron Letters* **1959,** No. 15, 19.

[95] Kochi, *J. Am. Chem. Soc.* **84,** 2785, 3271 (1962); Story, *Tetrahedron Letters* **1962,** 401.

[96] Kaeding, Kerlinger, and Collins, *J. Org. Chem.* **30,** 3754 (1965). Also see Kovacic and Kurz, *Tetrahedron Letters* **1966,** 2689.

[97] For reviews, see Walling, "Free Radicals in Solution," pp. 393–396, John Wiley & Sons, Inc., New York, 1957; and Gilbert, "Sulfonation and Related Reactions," pp. 126–131, Interscience Publishers, Inc., New York, 1965.

Chlorosulfenation may be accomplished by treatment with SCl_2 and ultraviolet light:[98]

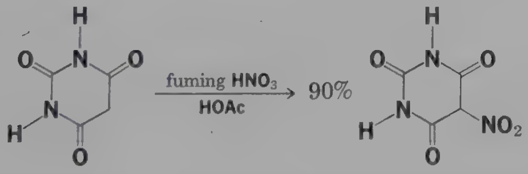
$$\mathrm{RH} + \mathrm{SCl_2} \xrightarrow{h\nu} \mathrm{RSCl}$$

D. Substitution by nitrogen

4-12 Nitration of paraffins

$$\mathrm{RH} + \mathrm{HNO_3} \xrightarrow{400^\circ} \mathrm{RNO_2}$$

Nitration of paraffins may be carried out in the gas phase, at about 400°, or in the liquid phase.[99] The reaction is not practical for the production of pure products for any alkane except methane. For other alkanes, not only does the reaction produce mixtures of the mono-, di-, and polynitrated alkanes, at every combination of positions, but extensive chain cleavage occurs, and to some extent the nitro products are further oxidized. As with reaction **4-1**, the order of preference is tertiary > secondary > primary, and allylic and benzylic positions are especially susceptible. Activated hydrogens (between two electron-withdrawing groups) are replaced under less drastic conditions and with much greater specificity,[100] for example,



The mechanism of this reaction has been the subject of considerable study, but there is no firm consensus of opinion, other than that the mechanism is of the free-radical type. It has been shown[101] that the vapor-phase nitration of methane is first order in nitric acid. The following scheme, with the initiation step irreversible and rate-determining, was the only one of eleven possible schemes considered which was consistent with the kinetic data:

Initiation $\mathrm{HNO_3} \longrightarrow \mathrm{HO\cdot} + \mathrm{NO_2}$

Propagation $\mathrm{RH} + \mathrm{HO\cdot} \longrightarrow \mathrm{R\cdot} + \mathrm{H_2O}$

$\mathrm{R\cdot} + \mathrm{HNO_3} \longrightarrow \mathrm{RNO_2} + \mathrm{HO\cdot}$

Termination $\mathrm{R\cdot} + \mathrm{HNO_3} \longrightarrow \mathrm{ROH} + \mathrm{NO_2}$

---

[98] Müller and Schmidt, *Chem. Ber.* **96**, 3050 (1963).

[99] For a review, see Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," pp. 216–234, The Macmillan Company, New York, 1964.

[100] For a review, see Kornblum, *Org. Reactions* **12**, 101–156 (1962), pp. 125–127.

[101] Godfrey, Hughes, and Ingold, *J. Chem. Soc.* **1965**, 1063.

This scheme shows only the principal steps. However, Titov has demonstrated[102] that nitric acid has no effect on paraffins in the absence of nitrogen dioxide (which is, of course, a free radical, since it has a total number of electrons which is odd). He thus has postulated that the principal product-forming steps are

$$\mathrm{RH + \cdot NO_2 \longrightarrow R\cdot + HNO_2}$$

$$\mathrm{R\cdot + \cdot NO_2 \longrightarrow RNO_2}$$

and that the only purpose of the nitric acid is to furnish a supply of nitrogen dioxide, perhaps by this reaction:

$$\mathrm{NO + 2HNO_3 \longrightarrow 3NO_2 + H_2O}$$

The NO is presumed to arise by one of the following pathways:

$$\mathrm{N_2O_3 \longrightarrow NO_2 + NO}$$

$$\mathrm{HNO_2 \longrightarrow HO\cdot + NO}$$

Other evidence for the radical character of the reaction (besides the conclusions drawn from the positions which are preferred) is the fact that racemization is found with optically active substrates[103] and the fact that rearrangement products were obtained in nitration of *tert*-butylbenzene[104] (the $\mathrm{Me_2CPhCH_2\cdot}$ radical is independently known to rearrange, see p. 790). The latter was impressive evidence because it had previously been reported that nitration proceeded *without* rearrangement.

Activated positions may also be nitrated by alkyl nitrites under alkaline conditions, so that the substrate is actually in the carbanionic form:[100]

$$\mathrm{-\overset{|}{\underset{|}{C}}|^{\ominus} + MeONO_2 \longrightarrow -\overset{|}{\underset{|}{C}}-NO_2 + OMe^-}$$

What is actually isolated under these alkaline conditions is the conjugate base of the nitro compound. Yields are not high. Of course, the mechanism in this case is not of the free-radical type at all but is electrophilic substitution, with respect to the carbon. With respect to the nitrogen it is nucleophilic substitution.

OS **I,** 390; **II,** 440, 512.

E. Attack by carbon. In these reactions a new carbon-carbon bond is formed, and they may be given the collective title *coupling reactions.* In each case an alkyl or aryl radical is generated and then combines with another radical (a termination process) or attacks an aromatic ring or olefin to give the coupling product.

4-13 Simple coupling at a susceptible position

$$\mathrm{2RH \xrightarrow{peroxides} R{-}R}$$

---

[102] Titov, *Tetrahedron* **19,** 557–580 (1963). This paper is a review of Titov's considerable work in this field.

[103] Schechter and Brain, *J. Am. Chem. Soc.* **85,** 1806 (1963).

[104] Duffin, Hughes, and Ingold, *J. Chem. Soc.* **1959,** 2734.

In this reaction, the peroxide decomposes to give a radical which abstracts a hydrogen from RH to give R·, which dimerizes. Dialkyl and diacyl peroxides have been used, as well as Fenton's reagent (p. 539). This reaction is far from general, although in certain cases respectable yields have been obtained. Among susceptible positions are those α to a phenyl group (especially if there is also an α-alkyl or α-chloro group),[105] an ether group,[106] a carbonyl group,[107] a cyano group,[108] a dialkylamino group,[109] or a carboxylic ester group, either the acid or alcohol side.[110] An example is the coupling of anisole:[106]

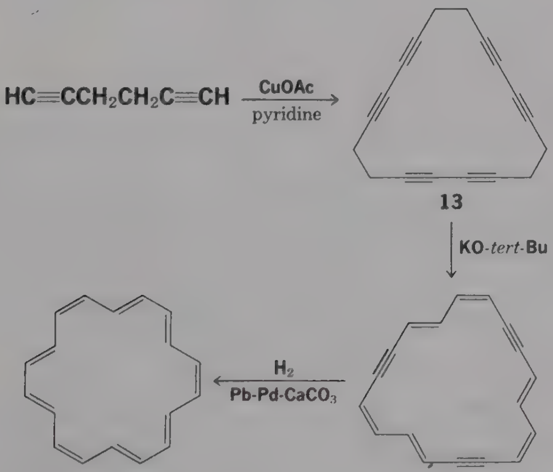
$$2\mathrm{Ph{-}O{-}CH_3} \xrightarrow{h\nu} \mathrm{Ph{-}O{-}CH_2CH_2{-}O{-}Ph}$$

OS **IV**, 367; **40**, 90.

4-14 Coupling of alkynes. The Glaser reaction

$$2\mathrm{R{-}C{\equiv}C{-}H} \xrightarrow[\text{pyridine}]{\mathrm{CuX_2}} \mathrm{R{-}C{\equiv}C{-}C{\equiv}C{-}R}$$

Alkynes which have a hydrogen on one of the triple-bond carbons may be coupled by heating with cupric salts in pyridine or a similar base. This reaction, which produces symmetrical diynes, is called the *Glaser reaction.*[111] The large-ring annulenes of Sondheimer et al. (see p. 52) were prepared by rearrangement and hydrogenation of cyclic polyynes, prepared by Glaser coupling of terminal diynes, for example;[112]



---

[105] McBay, Tucker, and Groves, *J. Org. Chem.* **24**, 536 (1959); Johnston and Williams, *J. Chem. Soc.* **1960**, 1168.

[106] Pfordte and Leuschner, *Ann.* **643**, 1 (1961). In this case ultraviolet light was used.

[107] Kharasch, McBay, and Urry, *J. Am. Chem. Soc.* **70**, 1269 (1948).

[108] Kharasch and Sosnovsky, *Tetrahedron* **3**, 97 (1958).

[109] Schwetlick, Jentzsch, Karl, and Wolter, *J. prakt. Chem.* [4] **25**, 95 (1964).

[110] Boguslavskaya and Razuvaev, *J. Gen. Chem. USSR* **33**, 1967 (1963).

[111] For a review, see Eglinton and McCrae, *Advan. Org. Chem.* **4**, 225–328 (1963).

[112] Sondheimer and Wolovsky, *J. Am. Chem. Soc.* **84**, 260 (1962); Sondheimer, Wolovsky, and Amiel, *J. Am. Chem. Soc.* **84**, 274 (1962).

13 is a cyclic trimer of 1,5-hexadiyne. The corresponding tetramers (C_{24}), pentamers (C_{30}), and hexamers (C_{36}) were also formed.

The Glaser reaction is of wide scope. Many functional groups may be present on the alkyne. The oxidation is usually quite specific for triple-bond hydrogen. The cuprous ion is a necessary intermediate, but apparently there is always enough present in cupric salts to make the reaction possible. Another common procedure is the use of cuprous salts in the presence of ammonia or ammonium chloride. Atmospheric oxygen, or some other oxidizing agent such as permanganate or hydrogen peroxide, is required in the latter procedure. This method is not satisfactory for cyclic coupling. Unsymmetrical diynes may be prepared by the *Cadiot-Chodkiewicz procedure:*[113]

$$\mathrm{R{-}C{\equiv}C{-}H + R'{-}C{\equiv}C{-}Br \xrightarrow{Cu^+} R{-}C{\equiv}C{-}C{\equiv}C{-}R' + HBr}$$

This may be regarded as a variation of reaction **0-83** (p. 355) but must have a different mechanism, since acetylenic halides give the reaction, but ordinary alkyl halides do not, and this is hardly compatible with a nucleophilic mechanism. However, the mechanism is not fully understood.

The mechanism of the Glaser reaction probably begins with loss of a proton

$$\mathrm{R{-}C{\equiv}C{-}H \xrightarrow[Cu^+]{base} R{-}C{\equiv}C^- + Cu^+}$$

since there is a base present and acetylenic protons are acidic. The last step is probably the coupling of two free radicals:

$$\mathrm{2R{-}C{\equiv}C\cdot \longrightarrow R{-}C{\equiv}C{-}C{\equiv}C{-}R}$$

but just how the carbanion becomes oxidized to the radical and what part the cuprous ion plays (other than forming the acetylide salt) are matters of considerable speculation,[114] and depend on the oxidizing agent. It is known, of course, that cuprous ion can form complexes with triple bonds.

OS **45,** 39.

4-15 Arylation of aromatic compounds by diazonium salts

$$\mathrm{ArH + Ar'N_2^+ \quad X^- \xrightarrow{OH^-} Ar{-}Ar'}$$

When the normally acidic solution of a diazonium salt is made alkaline, the aryl portion of the diazonium salt can couple with another aromatic ring. This is known as the *Gomberg* or *Gomberg-Bachmann reaction,*[115] and has been performed on several types of aromatic ring, including ferrocenes,[116] and on quinones. Yields are not high (usually under 40%) because of the many side reactions undergone by diazonium salts. The conditions of the Meerwein reaction (reaction **4-16**) have also been used.[117] When the Gomberg-Bachmann reaction is performed intramolecularly,

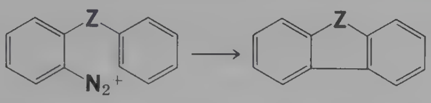
---

[113] Chodkiewicz, *Ann. chim.* (*Paris*) [13] **2,** 819 (1957).

[114] See the discussion in Ref. 113; and Clifford and Waters, *J. Chem. Soc.* **1963,** 3056.

[115] For reviews, see Bachmann and Hoffman, *Org. Reactions* **2,** 224–261 (1944); Dermer and Edmison, *Chem. Rev.* **57,** 77–122 (1957); Williams, "Homolytic Aromatic Substitution," pp. 27–34, 80–93, Pergamon Press, New York, 1960.

[116] Rosenblum, Howells, Banerjee, and Bennett, *J. Am. Chem. Soc.* **84,** 2726 (1962).



it is called the *Pschorr ring closure,*[118] and yields are usually somewhat higher. The reaction has been carried out for Z = CH=CH, CH_2CH_2, NH, C=O, CH_2, and quite a few others.

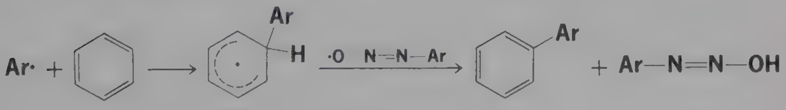
Other compounds with nitrogen-nitrogen bonds have been used instead of diazonium salts. Among these are N-nitroso amides [Ar—N(NO)—COR], triazenes, and azo compounds.

In each case the mechanism involves generation of an aryl radical from a *covalent* azo compound. In acid solution diazonium salts are ionic, and their reactions are polar. When they cleave, the product is an aryl cation (see p. 491). However, in neutral or basic solution, diazonium ions are converted to covalent compounds, and these cleave to give free radicals:[119]

$$\mathrm{Ar{-}N{=}N{-}Z} \longrightarrow \mathrm{Ar\cdot} + \mathrm{N{\equiv}N} + \mathrm{Z\cdot}$$

Under Gomberg-Bachmann conditions, the species which cleaves is the anhydride Ar—N=N—O—N=N—Ar:[120]

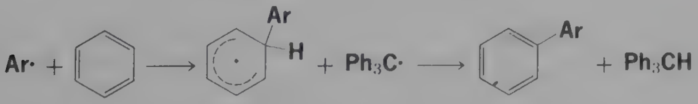
$$\mathrm{Ar{-}N{=}N{-}O{-}N{=}N{-}Ar} \longrightarrow \mathrm{Ar\cdot} + \mathrm{N_2} + \mathrm{\cdot O{-}N{=}N{-}Ar}$$



14

The aryl radical thus formed attacks the substrate to give the intermediate **14**, from which the radical Ar—N=N—O· abstracts hydrogen to give the product. When the reagent is phenylazotriphenylmethane (Ph_3C—N=N—Ar), the latter cleaves directly, and hydrogen is abstracted by the $Ph_3C\cdot$ radical:[121]

$$\mathrm{Ar{-}N{=}N{-}CPh_3} \longrightarrow \mathrm{Ar\cdot} + \mathrm{N_2} + \mathrm{Ph_3C\cdot}$$



14

---

[117] See, for example, Dickerman, Felix, and Levy, *J. Org. Chem.* **29**, 26 (1964).

[118] For reviews, see De Tar, *Org. Reactions* **9**, 409–462 (1957); Leake, *Chem. Rev.* **56**, 27–48 (1956).

[119] For a discussion of the mechanism of this cleavage, see Rüchardt and Merz, *Tetrahedron Letters* **1964**, 2431.

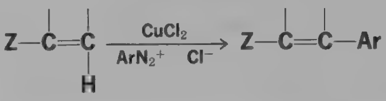
[120] Ref. 119; Eliel, Saha, and Meyerson, *J. Org. Chem.* **30**, 2451 (1965).

[121] Hey, Perkins, and Williams, *J. Chem. Soc.* **1965**, 110; Garst and Cole, *Tetrahedron Letters* **1963**, 679.

Although the triphenylmethyl radical is normally too unreactive to abstract hydrogens, it can do so in this case, because of the favorable energy change in the conversion of the radical **14** to a fully aromatic compound. In the case of N-nitroso amides, the situation is much less clear.[122] It is probable that in this case too, a covalent azo compound cleaves to give aryl radicals, but the process seems to be more complicated.[123]

OS **I**, 113; **IV**, 718.

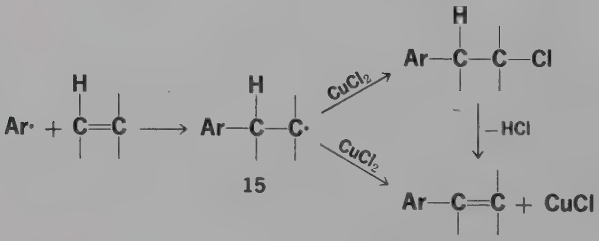
4-16 Arylation of activated olefins



$$\mathrm{Z{-}\overset{|}{C}{=}\underset{H}{\overset{|}{C}}} \xrightarrow[\mathrm{ArN_2^+\quad Cl^-}]{\mathrm{CuCl_2}} \mathrm{Z{-}\overset{|}{C}{=}\overset{|}{C}{-}Ar}$$

Olefins activated by an electron-withdrawing group (Z may be C=C, halogen, C=O, Ar, CN, etc.) may be arylated by treatment with a diazonium salt and a cupric chloride catalyst.[124] This is called the *Meerwein arylation reaction.* Addition of ArCl to the double bond (to give $\mathrm{Z{-}\underset{Cl}{\overset{|}{C}}{-}\underset{H}{\overset{|}{C}}{-}Ar}$) is a side reaction (reaction **5-26;** p. 614). The reaction gives best results on quinones, cinnamic acid derivatives, and other activated olefins, but it has been performed even on unactivated compounds such as ethylene and acetylene. The reaction may be carried out without the catalyst, but yields are lower.

The mechanism is probably of the free-radical type, with Ar· forming as in reaction **4-15,** and then[125]



The radical **15** may react with cupric chloride by two pathways, one of which leads to addition and the other to substitution. Even when the addition pathway is taken, however, the substitution product may still be formed by subsequent elimination of HCl.[126] In the case of the reaction between diazonium chlorides and α-bromostyrene, the substitution product was definitely formed by addition-elimination, since the product was *α-chloro*stilbene:[127]

---

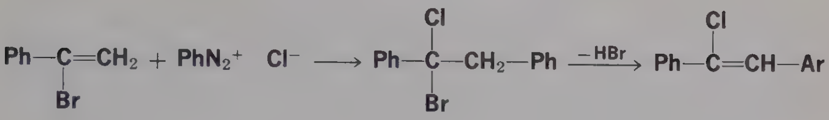
[122] See, for example, Brydon, Cadogan, Smith, and Thomson, *Chem. Commun.* **1967,** 727.

[123] See Chalfont and Perkins, *J. Am. Chem. Soc.* **89,** 3054 (1967); and Ref. 122.

[124] For a review, see Rondestvedt, *Org. Reactions* **11,** 189–260 (1960).

[125] Dickerman and Vermont, *J. Am. Chem. Soc.* **84,** 4150 (1962); Morrison, Cazes, Samkoff, and Howe, *J. Am. Chem. Soc.* **84,** 4152 (1962).

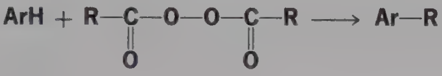
[126] For a discussion of the mechanism, see Zollinger, "Azo and Diazo Chemistry," pp. 162–165, Interscience Publishers, Inc., New York, 1961.



$$\mathrm{Ph{-}\underset{Br}{C}{=}CH_2 + PhN_2^+\ \ Cl^- \longrightarrow Ph{-}\overset{Cl}{\underset{Br}{C}}{-}CH_2{-}Ph \xrightarrow{-HBr} Ph{-}\overset{Cl}{C}{=}CH{-}Ar}$$

OS **IV,** 15.

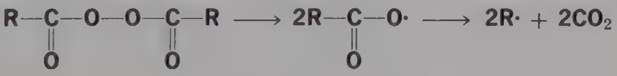
4-17 Alkylation and arylation of aromatic compounds by peroxides



$$\mathrm{ArH + R{-}\underset{O}{\underset{\|}{C}}{-}O{-}O{-}\underset{O}{\underset{\|}{C}}{-}R \longrightarrow Ar{-}R}$$

Arylation by peroxides is most often carried out with R = aryl, so that the net result is the same as in reaction **4-15,** though the reagent is different. It is used less often than reaction **4-15,** but the scope is similar. When R = alkyl, the scope is more limited. Only certain aromatic compounds, particularly those with two or more nitro groups, can be alkylated by this procedure. 1,4-Quinones may be alkylated with diacyl peroxides or with lead tetraacetate (methylation occurs with this reagent).

The mechanism involves attack on the substrate by free radicals formed by



$$\mathrm{R{-}\underset{O}{\underset{\|}{C}}{-}O{-}O{-}\underset{O}{\underset{\|}{C}}{-}R \longrightarrow 2R{-}\underset{O}{\underset{\|}{C}}{-}O\cdot \longrightarrow 2R\cdot + 2CO_2}$$

The attack is similar to that shown in reaction **4-15,** to give **14.** However, in this case, there is no relatively stable free radical (such as $\mathrm{Ph{-}N{=}N{-}O\cdot}$ or $\mathrm{Ph_3C\cdot}$) present to abstract hydrogen from **14,** which therefore dimerizes and disproportionates, as shown on page 524.

There are no *Organic Syntheses* references, but see OS **45,** 91, for a related reaction.

N_2 as Leaving Group.[128] In these reactions diazonium salts are cleaved to aryl radicals, either with the assistance of cuprous salts or by making the solution basic so that covalent azo compounds are present (which cleave to free radicals, p. 551).[129] Reactions **4-14** and **4-16** may also be regarded as belonging to this category with respect to the attacking compound. For nucleophilic substitutions of diazonium salts, see reactions **3-21** to **3-25** (pp. 512–513).

[127] Dombrovskii and Tashchuk, *J. Gen. Chem. USSR* **34,** 3393 (1964).

[128] For a review, see Cowdrey and Davies, *Quart. Rev.* (*London*) **6,** 358–379 (1952).

[129] For reviews, see Zollinger, Ref. 126, pp. 153–169; Belov and Kozlov, *Russ. Chem. Rev.* **32,** 59–75 (1963).

4-18 Replacement of the diazonium group by chlorine or bromine

$$ArN_2^+ + CuCl \longrightarrow ArCl$$

Treatment of diazonium salts with cuprous chloride or bromide leads to aryl chlorides or bromides, respectively. In either case the reaction is called the *Sandmeyer reaction.* The reaction may also be carried out with copper and HBr or HCl, in which case it is called the *Gatterman reaction* (not to be confused with reaction **1-17,** p. 417). The Sandmeyer reaction is not useful for the preparation of fluorides or iodides, but for bromides and chlorides it is of wide scope and is probably the best way of introducing bromine or chlorine into an aromatic ring. The yields are usually high.

The mechanism is by no means known with certainty but is believed to take the following course:[130]

$$ArN_2^+ \quad X^- + CuX \longrightarrow Ar\cdot + N_2 + CuX_2$$
$$Ar\cdot + CuX_2 \longrightarrow ArX + CuX$$

The first step involves a reduction of the diazonium ion by the cuprous ion, resulting in the formation of an aryl radical. In the second step, the aryl radical abstracts halogen from cupric chloride, reducing it. CuX is regenerated and is thus a true catalyst.

For the preparation of fluorides and iodides from diazonium salts, see reactions **3-24** (p. 513) and **3-23** (p. 512).

OS **I,** 135, 136, 162, 170; **II,** 130; **III,** 185; **IV,** 160. Also see OS **III,** 136; **IV,** 182.

4-19 Replacement of the diazonium group by nitro

$$ArN_2^+ + NaNO_2 \xrightarrow{Cu^+} ArNO_2$$

Nitro compounds may be formed in good yields by treatment of diazonium salts with sodium nitrite in the presence of cuprous ion. The reaction occurs only in neutral or alkaline solution. This is not usually called the Sandmeyer reaction, although, like reactions **4-18** and **4-20,** it was discovered by Sandmeyer. BF_4^- is often used as the negative ion, to avoid competition from the chloride ion. The mechanism is probably like that of reaction **4-18.**

OS **II,** 225; **III,** 341.

4-20 Replacement of the diazonium group by cyano

$$ArN_2^+ + CuCN \longrightarrow ArCN$$

---

[130] Dickerman, Weiss, and Ingberman, *J. Org. Chem.* **21,** 380 (1956), *J. Am. Chem. Soc.* **80,** 1904 (1958).

This reaction, also called the *Sandmeyer reaction,* is similar to reaction **4-18** in scope and mechanism. It is usually conducted in neutral solution to avoid liberation of HCN.

OS **I,** 514.

4-21 Aryl dimerization with diazonium salts

$$2\mathrm{ArN_2}^+ \xrightarrow[\text{or Cu + H}^+]{\mathrm{Cu}^+} \mathrm{Ar{-}Ar} + 2\mathrm{N_2} \qquad \text{or} \qquad \mathrm{Ar{-}N{=}N{-}Ar} + \mathrm{N_2}$$

When diazonium salts are treated with cuprous ion (or with copper and acid, in which case it is called the *Gatterman method*), two products are possible. If the ring contains electron-withdrawing groups, then the main product is the biaryl, but the presence of electron-donating groups leads mainly to the azo compound. This reaction is different from reaction **4-15** in that *both* aryl groups in the product originate from $\mathrm{ArN_2}^+$; that is, hydrogen is not a leaving group in this reaction.

OS **I,** 222; **IV,** 872. Also see OS **IV,** 273.

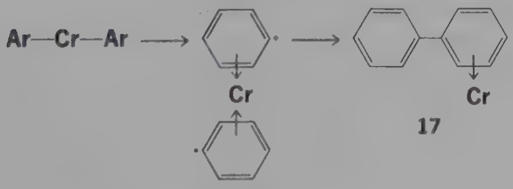
Metals as Leaving Groups

4-22 Coupling of organometallic compounds

$$2\mathrm{RMgX} \xrightarrow{\mathrm{CrCl_2}} \mathrm{R{-}R}$$

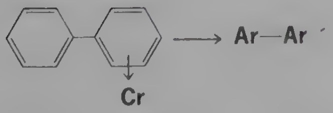
Many Grignard reagents have been coupled with transition-metal halides.[131] Besides $\mathrm{CrCl_2}$, many other halides have been used, among them $\mathrm{CrCl_3}$, $\mathrm{MnCl_2}$, $\mathrm{CoBr_2}$, $\mathrm{CuCl_2}$, etc. The salt is an oxidizing agent and becomes reduced. Both aryl and alkyl Grignard reagents give the reaction. For aryl Grignard reagents the following mechanism has been proposed:[132]

$$2\mathrm{ArMgBr} + \mathrm{CrCl_2} \longrightarrow \mathrm{Ar{-}Cr{-}Ar}$$



17

16



The first step of the reaction involves replacement of magnesium by the transition metal (this is an example of reaction **2-21,** p. 474). The diaryl-transition-metal compound then rearranges to a sandwich diradical (**16**), which couples to give **17**, in which the chromium, now reduced to zero oxidation state, is still complexed to one ring. **17** is decomposed by boiling in benzene.

---

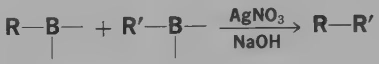
[131] For a review, see Kharasch and Reinmuth, "Grignard Reactions of Nonmetallic Substances," pp. 117–124, Prentice-Hall, Inc., Englewood Cliffs, N.J., 1954.

[132] Tsutsui, *Ann. N.Y. Acad. Sci.* **93,** 133–146 (1962).

Similar reactions, for both aryl and alkyl groups, may be carried out with organolithium compounds.[133]

Boron as Leaving Group

4-23 Coupling of boranes



$$\mathrm{R{-}\underset{|}{B}{-}} + \mathrm{R'{-}\underset{|}{B}{-}} \xrightarrow[\mathrm{NaOH}]{\mathrm{AgNO_3}} \mathrm{R{-}R'}$$

Alkylboranes may be coupled by treatment with silver nitrate and base.[134] Since alkylboranes are easily prepared from olefins (reaction **5-13**, p. 599), this is essentially a way of coupling and reducing olefins: in fact, olefins may be hydroborated and coupled in the same flask. For symmetrical coupling ($R = R'$), yields range from 60 to 80% for terminal olefins and from 35 to 50% for those with the double bond not at the end of a chain. Unsymmetrical coupling has also been carried out,[135] but with lower yields. The mechanism is probably of the free-radical type but has not yet been studied much.[136]

Halogen as Leaving Group. The conversion of RX to RH may occur by a free-radical mechanism but is treated at reaction **0-73** (p. 348).

Sulfur as Leaving Group

4-24 Desulfurization with Raney nickel

$$\mathrm{RSH} \xrightarrow[\mathrm{Ni}]{\mathrm{H_2}} \mathrm{RH}$$

$$\mathrm{RSR'} \xrightarrow[\mathrm{Ni}]{\mathrm{H_2}} \mathrm{RH} + \mathrm{R'H}$$

Thiols and thioethers, both alkyl and aryl, may be desulfurized by hydrogenolysis with Raney nickel.[137] The hydrogen is usually not applied externally, since Raney nickel already contains enough hydrogen for the reaction. Other sulfur compounds may be similarly desulfurized, among them:

Disulfides	$\mathrm{RSSR'} \longrightarrow \mathrm{RH} + \mathrm{R'H}$
Thioamides	$\mathrm{RCSNHR'} \longrightarrow \mathrm{RCH_2NHR'}$
Sulfoxides	$\mathrm{RSOR'} \longrightarrow \mathrm{RH} + \mathrm{R'H}$

---

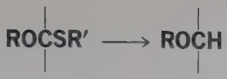
[133] Morizur, *Bull. Soc. chim. France* **1964**, 1331.

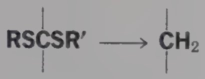
[134] For a review, see Brown, "Hydroboration," pp. 77–80, W. A. Benjamin, Inc., New York, 1962.

[135] Brown, Verbrugge, and Snyder, *J. Am. Chem. Soc.* **83**, 1001 (1961).

[136] Brown and Snyder, *J. Am. Chem. Soc.* **83**, 1002 (1961).

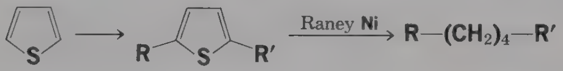
[137] For reviews, see Pettit and van Tamelen, *Org. Reactions* **12**, 356–529 (1962); and Hauptmann and Walter, *Chem. Rev.* **62**, 347–404 (1962).

Hemithioacetals 
$RO\overset{|}{\underset{|}{C}}SR' \longrightarrow RO\overset{|}{\underset{|}{C}}H$

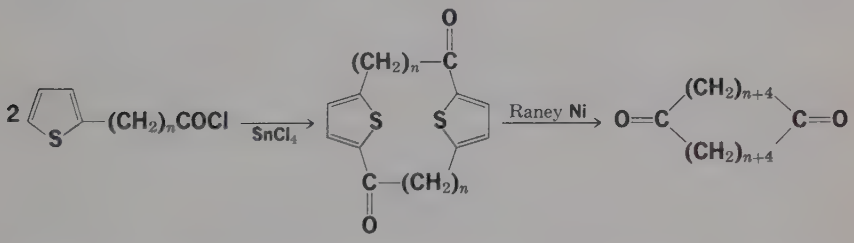
Dithioacetals 
$RS\overset{|}{\underset{|}{C}}SR' \longrightarrow \overset{|}{\underset{|}{C}}H_2$

The last reaction, which is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see reaction **9-34**, p. 891), can also give the olefin if an α hydrogen is present.[138] In most of the examples given, R may also be aryl. Other reagents have also been used.[139]

An important special case is desulfurization of thiophene derivatives (a special case of RSR reduction). This proceeds with concomitant reduction of the double bonds. Many otherwise difficultly accessible compounds have been made by alkylation of thiophene, followed by reduction:



An example is the following, which was accomplished for $n = 8$ and 9:[140]



The exact mechanism is still in doubt, though it is probably of the free-radical type.[141] It has been shown that reduction of thiophene proceeds through butadiene and butene, and not through butyl mercaptan or other sulfur compounds; that is, the sulfur is removed before the double bonds are reduced. This was demonstrated by isolation of the olefins, and the failure to isolate any potential sulfur-containing intermediates.[142]

OS **IV,** 638; **42,** 54.

Carbon as Leaving Group

4-25 Decarboxylative dimerization. The Kolbe reaction

$$2RCOO^- \xrightarrow{\text{electrolysis}} R{-}R$$

---

[138] Fishman, Torigoe, and Guzik, *J. Org. Chem.* **28,** 1443 (1963).

[139] For example, triethyl phosphite, by Hoffmann, Ess, Simmons, and Hanzel, *J. Am. Chem. Soc.* **78,** 6414 (1956); and sodium in liquid ammonia, by Truce, Tate, and Burdge, *J. Am. Chem. Soc.* **82,** 2872 (1960).

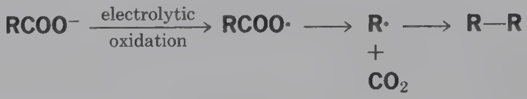
[140] Gol'dfarb, Taits, and Belen'kii, *J. Gen. Chem. USSR* **29,** 3526 (1959).

[141] Badger, Cheuychit, and Sasse, *J. Chem. Soc.* **1962,** 3235, 3241.

[142] Owens and Ahmberg, *Can. J. Chem.* **40,** 941 (1962).

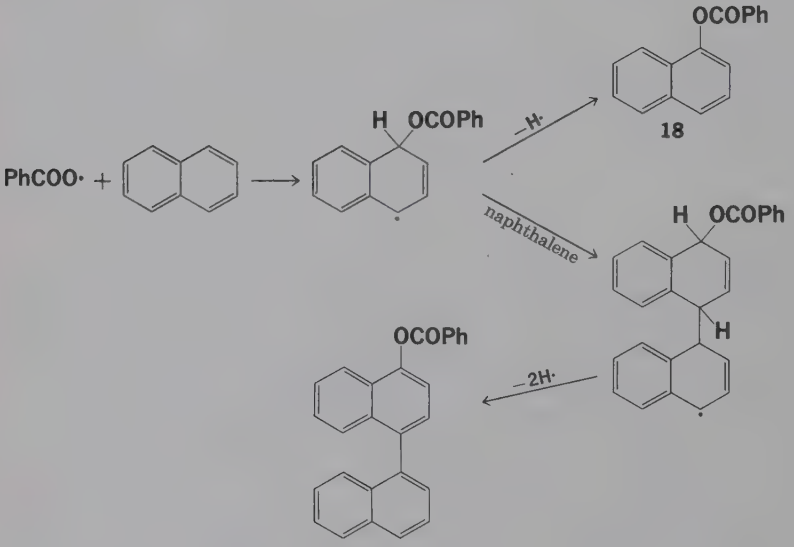
Electrolysis of carboxylate ions, which results in decarboxylation and combination of the resulting radicals, is called the *Kolbe reaction.*[143] It is used to prepare symmetrical R—R, where R is straight- or branched-chained, except that little or no yields are obtained when there is α branching. When R is aryl, the reaction fails. Many functional groups may be present, though many others inhibit the reaction.[143] The position of the functional group is important, too. Thus $F(CH_2)_4COO^-$ gives 45% $F(CH_2)_8F$, but $F(CH_2)_3COO^-$ gives no reaction. Unsymmetrical R—R′ have been made by coupling mixtures of acid salts.

A free-radical mechanism is involved:



$$RCOO^- \xrightarrow[\text{oxidation}]{\text{electrolytic}} RCOO\cdot \longrightarrow \underset{CO_2}{\overset{R\cdot}{+}} \longrightarrow R\text{—}R$$

Unlike many other organic oxidations, there is an actual loss of an electron, in an electrolytic process. Among the evidence for the free-radical character of this reaction is the fact that reaction of $PhCOO^-$ in the presence of naphthalene gave **18** and **19**, which are easily rationalized on the basis of attack by $PhCOO\cdot$.[144]



19

When the reaction is carried out in the presence of 1,3-dienes, additive dimerization may occur:[145]

$$2RCOO^- + CH_2{=}CH{-}CH{=}CH_2 \longrightarrow RCH_2CH{=}CHCH_2CH_2CH{=}CHCH_2R$$

---

[143] For reviews, see Weedon, *Quart. Rev. (London)* **6,** 380–398 (1952), *Advan. Org. Chem.* **1,** 1–34 (1960).

[144] Wilshire, *Australian J. Chem.* **16,** 432 (1963).

[145] Lindsey and Peterson, *J. Am. Chem. Soc.* **81,** 2073 (1959).

The radical R· adds to the conjugated system to give $RCH_2CH{=}CHCH_2\cdot$, which dimerizes. Another possible product is $RCH_2CH{=}CHCH_2R$, from coupling of the two kinds of radicals.[146]

OS **III**, 401; **41**, 24, 33.

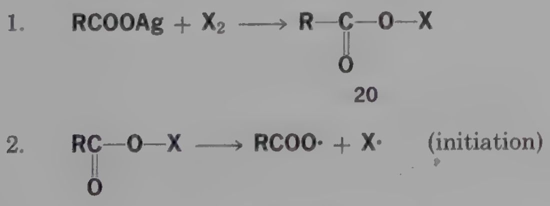
4-26 Decarboxylative bromination. The Hunsdiecker reaction

$$RCOOAg + Br_2 \longrightarrow RBr + CO_2 + AgBr$$

Reaction of a silver salt of a carboxylic acid with bromine is called the *Hunsdiecker reaction* and represents a way of decreasing a carbon chain by one unit.[147] The reaction is of wide scope, giving good results for normal-alkyl R from 2 to 18 carbons and for many branched R too, giving primary, secondary, and tertiary bromides. Many functional groups may be present as long as they are not α-substituted. R may also be aryl. However, if R contains unsaturation, the reaction seldom gives good results. Although bromine is the most often used halogen, chlorine and iodine have also been used.

When iodine is the reagent, then the ratio between the reactants is very important and determines the products. When a 1:1 ratio of salt to iodine is used, the product is the alkyl halide, as above. A 2:1 ratio, however, gives the ester RCOOR. This is called the *Simonini reaction* and is sometimes used to prepare esters. A 3:2 ratio gives both products: 1 mole of ester and 1 mole of halide from 3 moles of salt. The Simonini reaction may also be carried out with lead salts of acids.[148] A more convenient way to perform the Hunsdiecker reaction is by use of a mixture of the acid and mercuric oxide, instead of the salt, since the silver salt must be very pure and dry, and such pure silver salts are often not easy to prepare.[149] Another method involves treatment of the acid with lead tetraacetate and halide *ions* (chloride, bromide, or iodide).[150] The preparation of iodides has also been accomplished by treating the acid with iodine and lead tetraacetate in the presence of ultraviolet light.[151]

The mechanism of the Hunsdiecker reaction is believed to be as follows:



1. $RCOOAg + X_2 \longrightarrow R{-}\underset{\displaystyle \overset{\|}{O}}{C}{-}O{-}X$

20

2. $R\underset{\displaystyle \overset{\|}{O}}{C}{-}O{-}X \longrightarrow RCOO\cdot + X\cdot$ (initiation)

---

[146] Smith and Gilde, *J. Am. Chem. Soc.* **81**, 5325 (1959), **83**, 1355 (1961).

[147] For reviews, see Wilson, *Org. Reactions* **9**, 332–388 (1957); Johnson and Ingham, *Chem. Rev.* **56**, 219–269 (1957); Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," pp. 383–386, The Macmillan Company, New York, 1964.

[148] Bachman and Wittman, *J. Org. Chem.* **28**, 65 (1963).

[149] Cristol and Firth, *J. Org. Chem.* **26**, 280 (1961); Davis, Herynk, Carroll, Bunds, and Johnson, *J. Org. Chem.* **30**, 415 (1965).

[150] Kochi, *J. Am. Chem. Soc.* **87**, 2500 (1965), *J. Org. Chem.* **30**, 3265 (1965).

[151] Barton, Faro, Serebryakov, and Woolsey, *J. Chem. Soc.* **1965**, 2438.

$$3. \quad \text{RCOO}\cdot \longrightarrow \text{R}\cdot + \text{CO}_2$$

$$4. \quad \text{R}\cdot + \text{RCOOX} \longrightarrow \text{RX} + \text{RCOO}\cdot \qquad \text{(propagation)}$$

$$\text{etc.}$$

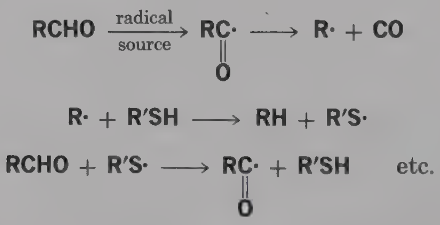
The first step is not a free-radical process, and its actual mechanism is not known. **20** is an acyl hypohalite and is presumed to be an intermediate, although it has never been isolated from the reaction mixture. Among the evidence for the mechanism outlined is that optical activity at R is lost (except when a neighboring bromine atom is present, see p. 525); if R is neopentyl, there is no rearrangement, which would certainly happen with a carbonium ion; and the side products, notably R—R, are consistent with a free-radical mechanism.

OS **III,** 578; **43,** 9.

4-27 Decarbonylation of aldehydes

$$\text{RCHO} \xrightarrow{\text{peroxides}} \text{RH}$$

Aldehydes may be decarbonylated by heating with di-*tert*-butyl peroxide, or other peroxides, usually in a solution containing a hydrogen donor such as a mercaptan. The reaction has also been initiated with light. In any case an initiator is required. The mechanism seems to be as follows (in the presence of mercaptans):[152]



$$\text{RCHO} \xrightarrow[\text{source}]{\text{radical}} \text{R}\underset{\substack{\|\\ \text{O}}}{\text{C}}\cdot \longrightarrow \text{R}\cdot + \text{CO}$$

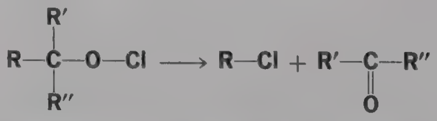
$$\text{R}\cdot + \text{R'SH} \longrightarrow \text{RH} + \text{R'S}\cdot$$

$$\text{RCHO} + \text{R'S}\cdot \longrightarrow \text{R}\underset{\substack{\|\\ \text{O}}}{\text{C}}\cdot + \text{R'SH} \qquad \text{etc.}$$

Aldehydes may also be decarbonylated by heating with catalysts such as palladium or chlorotris(triphenylphosphine)rhodium ($\text{RhCl(Ph}_3\text{P)}_3$).[153] The latter reagent also decarbonylates aromatic acyl halides to aryl halides:[154]

$$\text{ArCOCl} \longrightarrow \text{ArCl}$$

4-28 Decomposition of tertiary hypochlorites



$$\text{R}-\underset{\substack{|\\ \text{R''}}}{\overset{\substack{\text{R'}\\ |}}{\text{C}}}-\text{O}-\text{Cl} \longrightarrow \text{R}-\text{Cl} + \text{R'}-\underset{\substack{\|\\ \text{O}}}{\text{C}}-\text{R''}$$

---

[152] Slaugh, *J. Am. Chem. Soc.* **81,** 2262 (1959); Berman, Stanley, Sherman, and Cohen, *J. Am. Chem. Soc.* **85,** 4010 (1963).

[153] Tsuji and Ohno, *Tetrahedron Letters* **1965,** 3969; Tsuji, Ohno, and Kajimoto, *Tetrahedron Letters* **1965,** 4565.

[154] Blum, *Tetrahedron Letters* **1966,** 1605.

When tertiary hypochlorites are heated, they spontaneously decompose to alkyl halides and ketones.[155] The reaction may be regarded as substitution at R (of R_2COCl by Cl). Primary and secondary hypochlorites give the reaction under much milder conditions, but the group which cleaves in these cases is always hydrogen, so that the products are HCl and an aldehyde or ketone, and the reaction is better regarded as an elimination (of HCl) rather than as a substitution.

The mechanism has been formulated as follows:[156]

$$\begin{aligned} R_3C\text{—}O\text{—}Cl &\longrightarrow R_3C\text{—}O\cdot + Cl\cdot \\ R_3CO\cdot &\longrightarrow R_2C{=}O + R\cdot \\ R\cdot + R_3C\text{—}O\text{—}Cl &\longrightarrow RCl + R_3CO\cdot \end{aligned}$$

It may be noted that these three steps are exactly analogous to steps 2 to 4 of the mechanism of the Hunsdiecker reaction (**4-26**). The evidence for this mechanism is similar to that for reaction **4-26**: racemization, formation of R—R, etc.

---

[155] Cairns and Englund, *J. Org. Chem.* **21**, 140 (1956); Denney and Beach, *J. Org. Chem.* **24**, 108 (1959).

[156] Greene, *J. Am. Chem. Soc.* **81**, 2688 (1959); Greene, Savitz, Osterholtz, Lau, Smith, and Zanet, *J. Org. Chem.* **28**, 55 (1963).

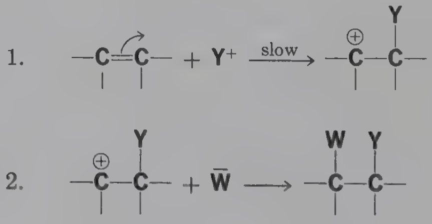
CHAPTER FIFTEEN

Addition to Carbon-Carbon Multiple Bonds

There are basically four ways in which addition to a double or triple bond may take place. Three of these are two-step processes, with initial attack by a nucleophile, an electrophile, or a free radical. The second step consists of combination of the resulting intermediate with, respectively, a positive species, a negative species, or a neutral entity. In the fourth type of mechanism, attack at the two sides of the double or triple bond is simultaneous. Which of the four mechanisms is operating in any given case is determined by the nature of the substrate, the reagent, and the reaction conditions. Some of the reactions in this chapter can take place by all four mechanisms.

MECHANISMS

Electrophilic Addition.[1] In this mechanism a positive species approaches the double or triple bond, and in the first step forms a bond by converting the π pair of electrons into a σ pair:



1. $-C=C- + Y^+ \xrightarrow{\text{slow}} -\overset{\oplus}{C}-\overset{Y}{C}-$

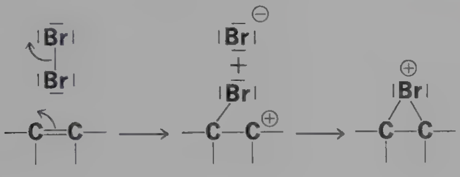
2. $-\overset{\oplus}{C}-\overset{Y}{C}- + \bar{W} \longrightarrow -\overset{W}{C}-\overset{Y}{C}-$

1

As in electrophilic substitution (p. 377), Y need not actually be a positive ion but may be the positive end of a dipole or an induced dipole, with the negative part breaking off either during the first step or shortly after. In any case, **1** has a positive charge on the other carbon. The second step, therefore, is a combination of **1** with a species carrying an electron pair, and usually bearing a negative charge. This step is the same as the second step of the S_N1 mechanism. There is evidence that **1** is not the actual intermediate ion in all cases. In brominations it is fairly certain that **1**, if it is formed at all, very rapidly cyclizes to a bromonium ion (**2**):

---

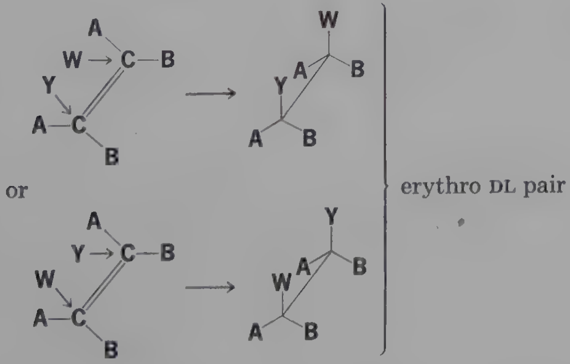
[1] For a monograph, see de la Mare and Bolton, "Electrophilic Additions to Unsaturated Systems," American Elsevier Publishing Company, New York, 1966.



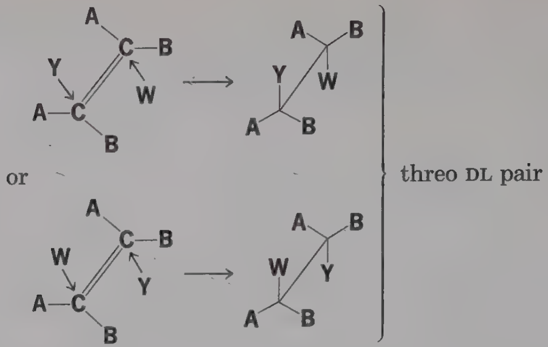
2

This intermediate is similar to those encountered in the neighboring-group mechanism of nucleophilic substitution, and it is likely that other potential neighboring groups (see p. 263) form similar intermediates, though the evidence is strongest for bromine. The attack of $\overline{W}$ on an intermediate like **2** is an S_N2 process.

In investigating the mechanism of addition to a double bond, perhaps the most useful type of information which may be obtained is the stereochemistry of the reaction. The two carbons of the double bond and the four atoms immediately attached to them are all in a plane (p. 14), and there are thus three possibilities. Y and W may enter from the same side of the plane, in which case the addition is stereospecific and cis; they may enter from opposite sides: stereospecific trans addition; or the reaction may be nonstereospecific. In order to determine which of these possibilities is occurring in a given reaction, the following type of experiment is often done: YW is added to the cis and trans isomers of an olefin of the form ABC=CBA. We may use the cis olefin as an example. If the addition is cis, the product will be the erythro DL pair, because each carbon has a 50% chance of being attacked by Y:

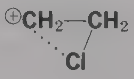


On the other hand, if the addition is trans, the threo DL pair will be formed:

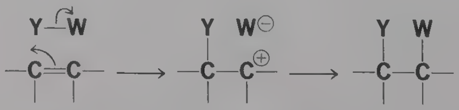


Of course, the trans isomer will give the threo pair if the addition is cis, and the erythro pair if it is trans. As with the similar experiment discussed on page 264, this experiment does not involve use of a polarimeter, and optical activity is not created, since none of the starting materials was optically active. The threo and erythro isomers have different physical properties. In the special case where Y = W (as in the addition of Br_2), then the "erythro pair" becomes a meso form. In addition to triple-bond compounds of the type $AC{\equiv}CA$, cis addition results in a cis olefin and trans addition in a trans olefin. By the definition given on page 101, addition to triple bonds cannot be stereospecific, though it can be, and often is, stereoselective.

It may easily be seen that, in reactions involving cyclic intermediates like **2**, addition must be trans, since the second step is an S_N2 process which must occur from the backside. It is not so easy to predict the stereochemistry for reactions involving **1**. If **1** has a relatively long life, the addition should be nonstereospecific, since there will be free rotation about the single bond. On the other hand there may be some factor which maintains the configuration, in which case W may come in from the same side or from the opposite side, depending on the circumstances. For example, it has been suggested[1a] that, for Y = Cl, the carbonium ion might be stabilized by an attraction for the Cl which does not involve a full bond:



The second group would then come in trans. A circumstance which would favor cis addition would be the formation of an ion pair after the addition of Y:[2]

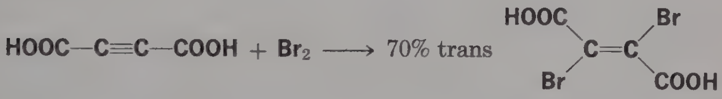


[1a] de la Mare, *Progr. Stereochem.* **1**, 114–120 (1954).

[2] Dewar, *Angew. Chem. Intern. Ed. Engl.* **3**, 245–249 (1964).

Since W is already on the same side of the plane as Y, collapse of the ion pair leads to cis addition. Another factor which might be responsible for trans addition is distortion of the substrate. It is known that ethylene, for example, in *excited* states is no longer planar. It has been suggested that trans addition may be the result of such distortion, or of vibrational distortion of the substrate.[3] A molecular-orbital argument involving orbital symmetries has been invoked to explain trans addition.[4]

It seems fairly certain that, when the attack is by Br^+ (or a carrier of it), the bromonium ion **2** is an intermediate, and the addition is trans. As long ago as 1912, McKenzie showed that treatment of maleic acid with bromine gave the DL pair of 2,3-dibromosuccinic acid, while fumaric acid (the trans isomer) gave the meso compound.[5] Many similar experiments have been performed since, with similar results. For triple bonds, stereoselective trans addition was shown even earlier. Bromination of dicarboxyacetylene gave 70% of the trans isomer:[6]



There is other evidence for mechanisms involving **2**. If the two bromines approach the double bond from opposite sides, then it is very unlikely that they could come from the same bromine molecule. This means that, if the reaction is performed in the presence of nucleophiles, some of these will compete in the second step with the bromide liberated from the bromine. It has been found, indeed, that treatment of ethylene with bromine in the presence of chloride ions gives some 1-chloro-2-bromoethane along with the dibromoethane.[7] Similar results were found when the reaction was carried out in the presence of nitrate ions and of water. It has been found, however, that the stereospecificity of bromine addition to stilbene depends on the dielectric constant of the solvent. In solvents of low dielectric constant, the addition was 90 to 100% trans, but with an increase in dielectric constant, the reaction became less stereospecific, until, at a dielectric constant of about 35, the addition was completely nonstereospecific.[8]

For electrophilic additions in which the electrophile is not Br^+ or a carrier of it, our knowledge is less certain. It seems that attack by I^+ and RS^+ also involves cyclic intermediates and hence trans addition.[9] When the electrophile is a proton, the cyclic intermediate is not possible. Examples are known of predominant cis, trans, and nonstereoselective addition of HX. It was found that treatment of 1,2-dimethylcyclohexene (**3**) with HBr and

---

[3] Burnelle, *Tetrahedron* **20**, 2403 (1964), **21**, 49 (1965).

[4] Fukui, *Tetrahedron Letters* **1965**, 2427.

[5] McKenzie, *J. Chem. Soc.* **101**, 1196 (1912).

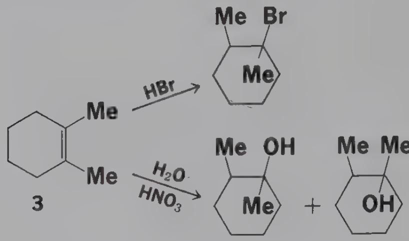
[6] Michael, *J. prakt. Chem.* **46**, 209 (1892).

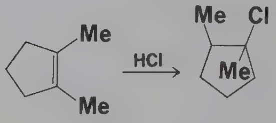
[7] Francis, *J. Am. Chem. Soc.* **47**, 2340 (1925).

[8] Buckles, Bader, and Thurmaier, *J. Org. Chem.* **27**, 4523 (1962).

[9] There is also evidence that Cl^+ may form cyclic intermediates: Peterson and Tao, *J. Am. Chem. Soc.* **86**, 4503 (1964); Fahey and Schubert, *J. Am. Chem. Soc.* **87**, 5172 (1965).

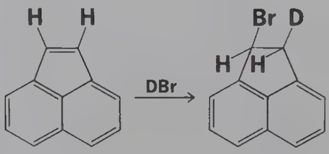
1,2-dimethylcyclopentene (**4**) with HCl gave predominant trans addition,[10] while addition of water to **3** gave equal amounts of the cis and trans alcohols:[11]





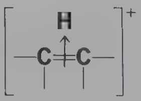
4

On the other hand, addition of DBr to acenaphthylene (**5**) and to indene and 1-phenylpropene gave predominant cis addition.[12]



5

In order to explain trans addition when the attack is by a proton, an initial complex of the form



$$\left[-\overset{\overset{H}{\uparrow}}{C{=}C}- \right]^+$$

has been invoked, and there is some evidence for it.[13] However, the strongest evidence for it was based on the Zucker-Hammett relationship (p. 225), and that has been shown to be invalid. The fact that some additions can be cis would seem to rule out such protonated complexes.[14] If there is a free carbonium ion intermediate in additions of H_2O, it cannot be reversibly formed, since unreacted olefin recovered after treatment with D_2SO_4 contained no (or very little) deuterium.[15] This has led some investigators to doubt that a free carbonium ion is involved in hydrations.[15]

---

[10] Hammond and Nevitt, *J. Am. Chem. Soc.* **76**, 4121 (1954); Hammond and Collins, *J. Am. Chem. Soc.* **82**, 4323 (1960).

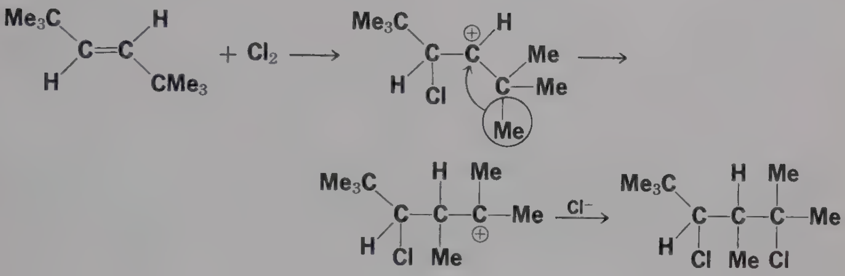
[11] Collins and Hammond, *J. Org. Chem.* **25**, 911 (1960).

[12] Dewar and Fahey, *J. Am. Chem. Soc.* **85**, 2245, 2248 (1963). For a review of cis addition of HX, see Ref. 2.

[13] See Purlee and Taft, *J. Am. Chem. Soc.* **78**, 5807 (1956).

[14] See Baliga and Whalley, *Can. J. Chem.* **42**, 1019 (1964), **43**, 2453 (1965).

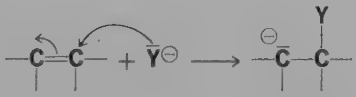
However, in order to show that free carbonium intermediates are formed in at least some reactions, we may cite the result of treatment of *trans*-1,2-di-*tert*-butylethylene with chlorine. The product was not the simple addition product expected, but **6**, which arose by rearrangement of the carbonium ion initially formed:[16]



6

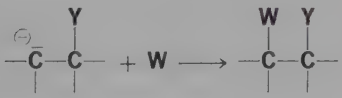
Nucleophilic Addition.[17] In the first step of nucleophilic addition a nucleophile brings its pair of electrons to one carbon atom of the double or triple bond, forcing the π electrons to become centered on the other carbon, creating a carbanion. The second step is combination of this carbanion with a positive species:

1.



7

2.



This mechanism is the same as the simple electrophilic one shown on page 562 except that the charges are reversed. When the olefin contains a good leaving group (as defined for nucleophilic substitution, p. 290), substitution is a side reaction (this is nucleophilic substitution at a vinyl substrate, see p. 278). There are at least five other types of side reactions which intermediates like **7** can undergo.[18]

In the special case of addition of HY to a substrate of the form $-\underset{|}{C}=\underset{|}{C}-Z$, where Z = CHO, COR (including quinones), COOR, $CONH_2$, CN, NO_2, SOR, SO_2R, etc., addition nearly always follows a nucleophilic mechanism, with Y^- bonding with the carbon *away* from the Z group, e.g.,

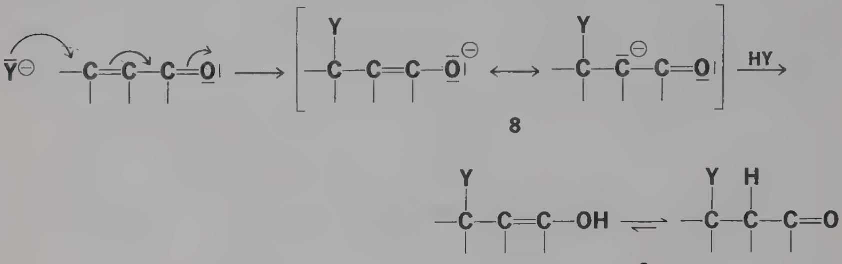
---

[15] Deno, Kish, and Peterson, *J. Am. Chem. Soc.* **87**, 2157 (1965).

[16] Puterbaugh and Newman, *J. Am. Chem. Soc.* **81**, 1611 (1959).

[17] For a review, see Patai and Rappoport, in Patai, "The Chemistry of Alkenes," pp. 469–584, Interscience Publishers, Inc., New York, 1964.

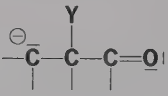
[18] Patai and Rappoport, *J. Chem. Soc.* **1962**, 377, 383, 392, 396; Ref. 17.



8

9

Protonation of the enolate ion **8** is chiefly at the oxygen, which is more negative than the carbon, but this produces the enol **9**, which tautomerizes. So, although the net result of the reaction is addition to a carbon-carbon double bond, the *mechanism* is 1,4 nucleophilic addition to the C=C—C=O (or similar) system and is thus very similar to the mechanism of addition to carbon-oxygen double and similar bonds (see Chapter 16). When Z is CN or a C=O group, then it is also possible for Y^- to attack at *this* carbon, and this reaction sometimes competes. When it happens, it is called 1,2 addition. Y^- never attacks at the 3-position, since the resulting carbanion would have no resonance stabilization:



Perhaps the most important substrate of this type is acrylonitrile, and 1,4 addition to it is called *cyanoethylation,* because the Y is cyanoethylated:[19]

$$H_2C{=}CH{-}CN + HY \longrightarrow Y{-}CH_2{-}CH_2{-}CN$$

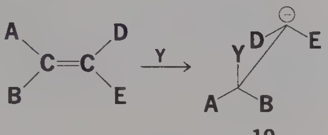
With any substrate, when Y is an ion of the type $Z{-}\overset{\ominus}{\bar{C}}R_2$ (Z is as defined on p. 357; R may be alkyl, aryl, hydrogen, or another Z), then the reaction is called the *Michael reaction* (see reaction **5-15**). In this book we shall call all other reactions which follow this mechanism *Michael-type additions.* Systems of the type C=C—C=C—Z may give 1,2, 1,4, or 1,6 addition.[20] Even 1,8 addition has been found with suitable substrates. Michael-type reactions are reversible, and compounds of the type YCH_2CH_2Z may often be decomposed to YH and $CH_2{=}CHZ$ by heating, either with or without alkali.

---

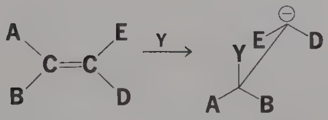
[19] For a review of cyanoethylations, see Bruson, *Org. Reactions* **5**, 79–135 (1949). For a review of cyanoethylations with compounds from which acrylonitrile is generated *in situ* (for example, $ClCH_2CH_2CN$), and of the reverse of cyanoethylation (decyanoethylation), see Butskus, *Russ. Chem. Rev.* **30**, 583–598 (1961).

[20] For a review of 1,6 Michael-type additions, see Ralls, *Chem. Rev.* **59**, 329–344 (1959).

If the mechanism for nucleophilic addition is the simple carbanion mechanism outlined on page 567, then the addition should be nonstereospecific, though it might well be stereoselective (see p. 101 for the distinction). For example, the cis and trans forms of an olefin ABC=CDE would give, respectively, **10** and **11**.



10



11

If the carbanion has even a short lifetime, then **10** and **11** will assume the most favorable conformation before the attack of W. This is of course the same for both of them, and when W attacks, the same product will result from each. This will be one of two possible diastereomers, so the reaction will be stereoselective; but since the cis and trans isomers do not give rise to different isomers, it will not be stereospecific. Unfortunately, this prediction has not been tested on open-chain olefins. Except for Michael-type substrates, the stereochemistry of nucleophilic addition to double bonds has been studied only in cyclic systems where only the cis isomer exists. In these cases the reaction has been shown to be stereoselective, with cis addition reported in some cases[21] and trans addition in others.[22] When the reaction is performed on a Michael-type substrate, C=C—Z, then the hydrogen does not arrive at the carbon directly, but only through a tautomeric equilibrium. The product will naturally assume the most thermodynamically stable configuration, without relation to the direction of original attack of Y. For obvious reasons, additions to triple bonds cannot be stereospecific. As with electrophilic additions, nucleophilic additions to triple bonds are usually stereoselective and trans,[23] though cis addition[24] and nonstereoselective addition[25] have also been reported.

[21] For example, Truce and Levy, *J. Org. Chem.* **28,** 679 (1963).

[22] For example, Truce and Levy, *J. Am. Chem. Soc.* **83,** 4641 (1961); Zefirov, Yur'ev, Prikazchikova, and Bykhovskaya, *J. Gen. Chem. USSR* **33,** 2100 (1963).

[23] Truce, Boudakian, Heine, and McManimie, *J. Am. Chem. Soc.* **78,** 2743 (1956); Truce and Simms, *J. Am. Chem. Soc.* **78,** 2756 (1956); Shostakovskii, Chekulaeva, Kondrat'eva, and Lopatin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1962,** 2118.

[24] Truce, Goldhamer, and Kruse, *J. Am. Chem. Soc.* **81,** 4931 (1959); Truce and Heine, *J. Am. Chem. Soc.* **79,** 5311 (1957); Dolfini, *J. Org. Chem.* **30,** 1298 (1965); Winterfeldt and Preuss, *Chem. Ber.* **99,** 450 (1966).

[25] Gracheva, Laba, Kul'bovskaya, and Shostakovskii, *J. Gen. Chem. USSR* **33,** 2431 (1963).

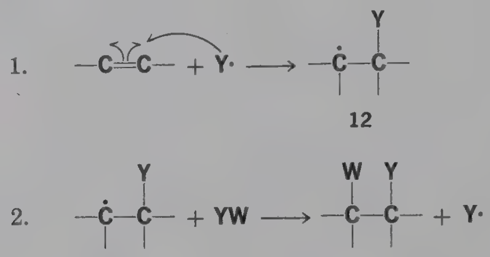
Free-radical Addition.[26] The mechanism of free-radical addition follows the pattern discussed in Chapter 14 (pp. 521–522). A radical is generated by

$$\mathrm{YW} \xrightarrow[\text{dissociation}]{h\nu \text{ or spontaneous}} \mathrm{Y}\cdot + \mathrm{W}\cdot$$

or

$$\mathrm{R}\cdot \text{ (from some other source)} + \mathrm{YW} \longrightarrow \mathrm{RW} + \mathrm{Y}\cdot$$

Propagation then occurs by

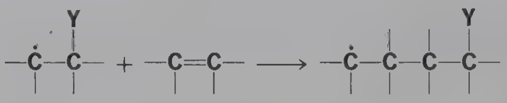


$$1.\quad -\mathrm{C}{=}\mathrm{C}- + \mathrm{Y}\cdot \longrightarrow -\dot{\mathrm{C}}-\overset{\mathrm{Y}}{\mathrm{C}}-$$

12

$$2.\quad -\dot{\mathrm{C}}-\overset{\mathrm{Y}}{\mathrm{C}}- + \mathrm{YW} \longrightarrow -\overset{\mathrm{W}}{\mathrm{C}}-\overset{\mathrm{Y}}{\mathrm{C}}- + \mathrm{Y}\cdot$$

Termination of the chain may occur in any of the ways discussed in Chapter 14. If **12** adds to another olefin molecule



$$-\dot{\mathrm{C}}-\overset{\mathrm{Y}}{\mathrm{C}}- + -\mathrm{C}{=}\mathrm{C}- \longrightarrow -\dot{\mathrm{C}}-\mathrm{C}-\mathrm{C}-\overset{\mathrm{Y}}{\mathrm{C}}-$$

a dimer is formed. This may now add to still another, and long chains may be built up. This is the mechanism of free-radical polymerization.

The free-radical addition mechanism just outlined predicts that the addition should be nonstereospecific, at least if **12** has any but an extremely short half-life. However, the reactions may be stereoselective, for reasons similar to those discussed for nucleophilic addition on page 569.[27] Many free-radical additions have been found to be stereoselective, though not all. For example, addition of HBr to 1-bromocyclohexene gave only *cis*-1,2-dibromocyclohexane and none of the trans isomer (trans addition),[28] and propyne (at −78 to −60°) gave only *cis*-1-bromopropene (trans addition).[29] However, stereospecificity has been found only in a few cases. The most important of these is addition of HBr to 2-bromo-2-butene under free-radical conditions at −80°. Under these conditions, the cis isomer gave 92% of the meso addend, while the trans isomer gave mostly the DL pair.[30] This stereospecificity disappeared at room temperature, where both olefins gave the same mixture of products (about 78% of the DL pair and 22% of the meso form), so that the addition was still stereoselective but no longer stereospecific. The stereospecificity at low temperatures is probably caused by a stabilization of the intermediate radical through the formation of a bridged bromine radical, of the type mentioned on page 525:

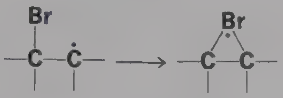
---

[26] For a monograph on this subject, see Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," The Macmillan Company, New York, 1964. Other books with much of interest in this field are by Pryor, "Free Radicals," McGraw-Hill Book Company, New York, 1965, and Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, 1957. Review articles are by Walling and Huyser, *Org. Reactions* **13**, 91–149 (1963); Stacey and Harris, *Org. Reactions* **13**, 150–376 (1963); Cadogan and Hey, *Quart. Rev.* (*London*) **8**, 308–329 (1954); and Cadogan and Perkins, in Patai, "The Chemistry of Alkenes," pp. 585–632, Interscience Publishers, Inc., New York, 1964.

[27] For a review of the stereochemistry of free-radical addition, see Bohm and Abell, *Chem. Rev.* **62**, 599–609 (1962).

[28] Goering, Abell, and Aycock, *J. Am. Chem. Soc.* **74**, 3588 (1952).

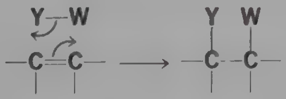
[29] Skell and Allen, *J. Am. Chem. Soc.* **80**, 5997 (1958).



This species is similar to the bromonium ion, which is responsible for trans addition in the electrophilic mechanism (p. 564). Further evidence for the existence of such bridged radicals was obtained by addition of Br· to olefins at 77°K. Electron-spin-resonance spectra of the resulting species were consistent with bridged structures.[31] There is evidence that iodine may form similar bridges: free-radical addition of I_2 at −42° is stereospecific and trans.[32] However, addition of RSH to olefins, even at −78°, is not stereospecific, though it is stereoselective.[33]

As mentioned previously, trans addition of HBr to triple bonds occurs at −78 to −60°.[29] However, at room temperature this reaction, whether conducted in the liquid or in the vapor phase, is nonstereoselective. It has been shown that this is only apparent: that the reaction is still stereoselective, but that isomerization occurs after the initial product is formed.[34] Stereoselective cis addition has been demonstrated in the reaction between 1-bromopropyne and HBr.[35]

Cyclic Mechanisms. There are some addition reactions where the initial attack is not on one side of the double bond, but both sides are attacked simultaneously. Some of these are four-center mechanisms, which follow this pattern:



---

[30] Goering and Larsen, *J. Am. Chem. Soc.* **79**, 2653 (1957), **81**, 5937 (1959). Also see Skell and Allen, *J. Am. Chem. Soc.* **81**, 5383 (1959); Skell and Freeman, *J. Org. Chem.* **29**, 2524 (1964).

[31] Abell and Piette, *J. Am. Chem. Soc.* **84**, 916 (1962).

[32] Skell and Pavlis, *J. Am. Chem. Soc.* **86**, 2965 (1964). The conclusion that iodine forms such bridges has been disputed by Benson, Golden, and Egger [*J. Chem. Phys.* **42**, 4265 (1965)], who hold that addition of I_2 is concerted.

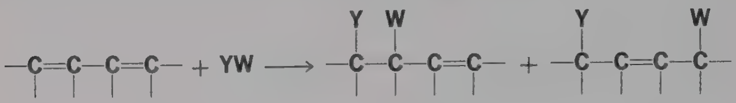
[33] Skell and Allen, *J. Am. Chem. Soc.* **82**, 1511 (1960); Neureiter and Bordwell, *J. Am. Chem. Soc.* **82**, 5354 (1960).

[34] Skell and Allen, *J. Am. Chem. Soc.* **86**, 1559 (1964).

[35] Bergel'son, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1960**, 1145.

In others there is a five- or a six-membered transition state. In these cases the addition to the double or triple bond must be cis. The most important reaction of this type is the Diels-Alder reaction (**5-34**).

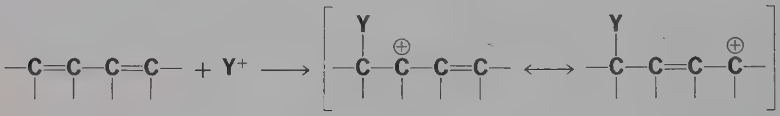
Addition to Conjugated Systems. When electrophilic addition is carried out on a compound which has two double bonds in conjugation, then a 1,2 addition product (**13**) is often obtained, but in most cases, there is also a 1,4 addition product (**14**), often in much larger yield:



$$-\underset{|}{C}=\underset{|}{C}-\underset{|}{C}=\underset{|}{C}- + YW \longrightarrow -\overset{\overset{Y}{|}}{\underset{|}{C}}-\overset{\overset{W}{|}}{\underset{|}{C}}-\underset{|}{C}=\underset{|}{C}- + -\overset{\overset{Y}{|}}{\underset{|}{C}}-\underset{|}{C}=\underset{|}{C}-\overset{\overset{W}{|}}{\underset{|}{C}}-$$

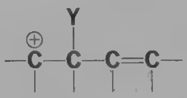
13 **14**

If the diene is unsymmetrical, then there may be two 1,2 addition products. The competition between two types of addition product comes about because the carbonium ion resulting from attack by Y^+ is a resonance hybrid, with partial positive charges at the 2- and 4-positions:



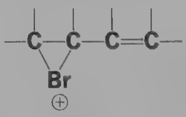
$$-\underset{|}{C}=\underset{|}{C}-\underset{|}{C}=\underset{|}{C}- + Y^+ \longrightarrow \left[-\overset{\overset{Y}{|}}{\underset{|}{C}}-\overset{\oplus}{\underset{|}{C}}-\underset{|}{C}=\underset{|}{C}- \longleftrightarrow -\overset{\overset{Y}{|}}{\underset{|}{C}}-\underset{|}{C}=\underset{|}{C}-\overset{\oplus}{\underset{|}{C}}-\right]$$

W^- may then attack either position. The original attack of Y^+ is always at the end of the conjugated system, because an attack at a middle carbon would give a carbonium ion unstabilized by resonance:

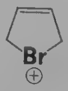


$$-\overset{\oplus}{\underset{|}{C}}-\overset{\overset{Y}{|}}{\underset{|}{C}}-\underset{|}{C}=\underset{|}{C}-$$

In the case of electrophiles like Br^+, which can form cyclic intermediates, both 1,2 and 1,4 addition products may be rationalized as stemming from an intermediate like **15**. Direct S_N2 attack by W^- would give the 1,2 product, while the 1,4 product could be formed by attack at the 4-position, by an S_N2'-type mechanism (see p. 271). Intermediates like **16** have been postulated,



15



16

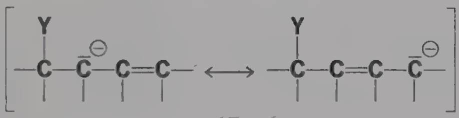
but ruled out for Br and Cl by the observation that chlorination or bromination of butadiene gives trans 1,4 products.[36] If an ion like **16** were the intermediate, the 1,4 products would have to have the cis configuration.

---

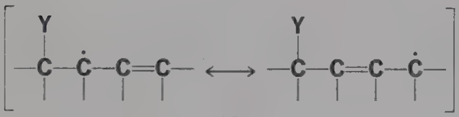
[36] Mislow and Hellman, *J. Am. Chem. Soc.* **73**, 244 (1951); Mislow, *J. Am. Chem. Soc.* **75**, 2512 (1953).

In most cases there is obtained more 1,4 than 1,2 addition product. This may be a consequence of thermodynamic control of products, as against kinetic. In most cases, under the reaction conditions, **13** is converted to a mixture of **13** and **14** which is richer in **14**. That is, either isomer gives the same mixture of both, which contains more **14**. It was found that at low temperatures, butadiene and HCl gave only 20 to 25% 1,4 adduct, while at high temperatures, where attainment of equilibrium is more likely, the mixture contained 75% 1,4 product.[37]

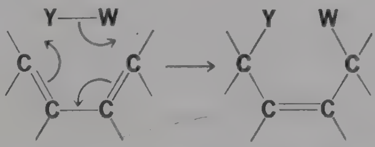
Addition to conjugated systems may also be accomplished by any of the other three mechanisms. In each case there is a competition between 1,2 and 1,4 addition. In the case of nucleophilic or free-radical attack, the intermediates (**17** and **18**) are resonance hybrids and behave like the intermediate from electrophilic attack. Dienes may give 1,4 addition by a cyclic mechanism in this way:



17



18



Other conjugated systems, including trienes, enynes, diynes, etc., have been studied much less, but behave similarly.[38]

ORIENTATION AND REACTIVITY

Reactivity. Electron-donating groups increase the reactivity of a double bond toward electrophilic addition, and electron-withdrawing groups decrease it. This is illustrated in Tables 1 and 2. As a further illustration it may be mentioned that the reactivity toward electrophilic addition of a group of olefins increased in the order $CCl_3CH{=}CH_2 < Cl_2CHCH{=}CH_2 < ClCH_2CH{=}CH_2 < CH_3CH_2{=}CH_2$.[39] For nucleophilic addition the situa-

---

[37] Kharasch, Kritchevsky, and Mayo, *J. Org. Chem.* **2**, 489 (1938).

[38] For reviews of addition to conjugated enynes, see Petrov, *Russ. Chem. Rev.* **29**, 489–509 (1960); and Taylor, *Chem. Rev.* **67**, 317–359 (1967), pp. 329–331.

[39] Shelton and Lee, *J. Org. Chem.* **25**, 428 (1960).

TABLE 1. Relative reactivity of some olefins toward bromine in acetic acid at 24°[40]

Olefin	*Relative rate*
$PhCH{=}CH_2$	Very fast
$PhCH{=}CHPh$	18
$CH_2{=}CHCH_2Cl$	1.6
$CH_2{=}CHCH_2Br$	1.0
$PhCH{=}CHBr$	0.11
$CH_2{=}CHBr$	0.0011

tion is reversed. These reactions are best carried out on substrates containing three or four electron-withdrawing groups, two of the most common being $F_2C{=}CF_2$[41] and $(NC)_2C{=}C(CN)_2$.[42] The effect of substituents is so great that it is possible to make the statement that *simple olefins do not react by the nucleophilic mechanism and polyhalo or polycyano olefins do not react by the electrophilic mechanism.* There are some reagents which attack only as nucleophiles (e.g., ammonia), and these add only to substrates susceptible to nucleophilic attack. Other reagents attack only as electrophiles, and, for example, $F_2C{=}CF_2$ does not react with these. In still other cases, the same reagent reacts with a simple olefin by the electrophilic mechanism and with a polyhalo olefin by a nucleophilic mechanism. For example, Cl_2 and HF are normally electrophilic reagents, but it has been shown that Cl_2 adds to $(NC)_2C{=}CHCN$ with an initial attack by Cl^-[43] and that HF adds to $F_2C{=}CClF$ with an initial attack by F^-.[44] Compounds which have a double bond conjugated with a Z group (as defined on p. 568) nearly always react by a nucleophilic mechanism. These are actually 1,4 additions, as discussed on page 568. The readiness with which C=C—Z compounds undergo Michael-type reactions, and the yields obtained diminish

[40] From de la Mare, *Quart. Rev.* (*London*) **3,** 126–145 (1949), p. 145.

[41] See especially England, Melby, Dietrich, and Lindsey, *J. Am. Chem. Soc.* **82,** 5116 (1960).

[42] For a review of additions to this compound, see Cairns and McKusick, *Angew. Chem.* **73,** 520–525 (1961).

[43] Dickinson, Wiley, and McKusick, *J. Am. Chem. Soc.* **82,** 6132 (1960).

[44] Miller, Fried, and Goldwhite, *J. Am. Chem. Soc.* **82,** 3091 (1960).

[45] Dubois and Mouvier, *Tetrahedron Letters* **1963,** 1325.

TABLE 2. Relative reactivity of some olefins toward bromine in methanol[45]

Olefin	*Relative rate*
$CH_2{=}CH_2$	3.0×10
$CH_3CH_2CH{=}CH_2$	2.9×10^3
cis-$CH_3CH_2CH{=}CHCH_3$	1.3×10^5
$(CH_3)_2C{=}C(CH_3)_2$	2.8×10^7

in the order Z = CHO, COR, COOR, CN, NO_2.[46] When such reactions are performed on Z—C=C—Z′, then this order controls the position of attack, so that, for example, PhCOCH=CHCN is attacked at the carbon adjacent to the CN.[47]

It seems obvious that electron-withdrawing groups enhance nucleophilic substitution and inhibit electrophilic substitution because they lower the electron density of the double bond. This is probably true, and yet similar reasoning does not apply to a comparison between double and triple bonds. There is a higher concentration of electrons between the carbons of a triple bond than there is in a double bond, and yet triple bonds are *less* subject to electrophilic attack and *more* subject to nucleophilic attack than are double bonds.[48] This statement is not universally true, but it does hold in most cases. In compounds containing both double and triple bonds (nonconjugated), bromine, an electrophilic reagent, always adds to the double bond.[49] On the other hand, addition of hydrogen halides gives results that are far from simple. In some cases (both conjugated and nonconjugated) the electrophilic H^+ predominantly attacks the double bond, and in other cases the triple bond.[50] Which bond is attacked seems to depend on the state of alkylation. When the triple bond is of the form HC≡C—, it is the bond exclusively or predominantly attacked by H^+, but internal triple bonds are not so preferred. With conjugated enynes mixtures are commonly obtained. Thus bromination of vinylacetylene gives all possible dibromides.[49]

Still, it is true that triple bonds are more susceptible to nucleophilic and less to electrophilic attack than are double bonds, in spite of their higher electron density. One explanation for this is that the electrons in the triple bond are held more tightly because of the smaller carbon-carbon distance, and it is thus harder for an attacking electrophile to pull out a pair. There is evidence from far-ultraviolet spectra to support this conclusion.[51] Another possible explanation is that vinyl cations are less stable than alkyl cations, but vinyl carbanions are more stable than alkyl carbanions.

Free-radical additions may occur with any type of substrate. The determining factor is the presence of a free-radical attacking species. Some reagents (for example, HBr, RSH) attack by ionic mechanisms if no initiator is present, but in the presence of a free-radical initiator, the mechanism changes and the addition is of the free-radical type. Nucleophilic radicals, like $CH_3\cdot$ (see p. 528), behave like nucleophiles, in that the rate is increased by the presence of electron-withdrawing groups in the substrate.[52] The reverse is true for electrophilic radicals.

Conjugated dienes are less reactive than simple olefins to electrophilic attack,[53] but more reactive to free-radical attack.

---

[46] Henecka, *Chem. Ber.* **81,** 197 (1948).

[47] Nesmeyanov, Rybinskaya, and Rybin, *Bull. Acad. Sci. USSR, Div. Chem. Soc.* **1961,** 2013.

[48] For discussions of this, see Bohlmann, *Angew. Chem.* **69,** 82 (1957); Miller, *J. Org. Chem.* **21,** 247 (1956); Daniels and Bauer, *J. Chem. Educ.* **35,** 444 (1958).

[49] Petrov, *Russ. Chem. Rev.* **29,** 489–509 (1960).

[50] Petrov and Porfir'eva, *J. Gen. Chem. USSR* **33,** 3142 (1963).

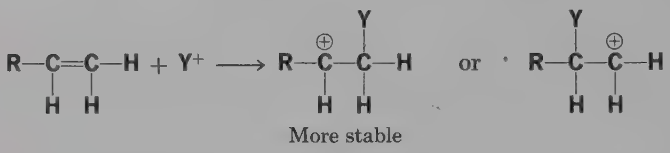
[51] Walsh, *Quart. Rev. (London)* **2,** 73–91 (1948).

[52] Herk, Stefani, and Szwarc, *J. Am. Chem. Soc.* **83,** 3008 (1961).

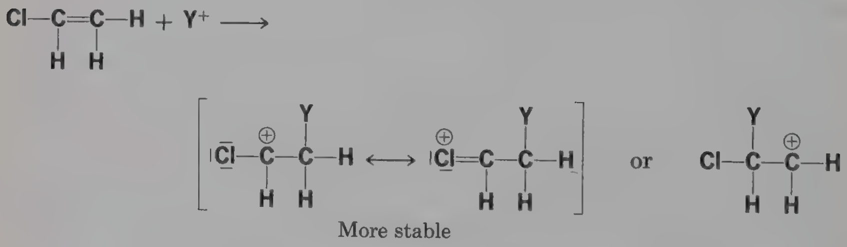
[53] Petrov and Porfir'eva, *J. Gen. Chem. USSR* **32,** 748 (1962).

Steric influences are important in some cases. In catalytic hydrogenation, where the substrate must be adsorbed onto the catalyst surface, the reaction becomes more difficult with increasing substitution. It has been shown that alkyl groups affect the rate of electrophilic substitution in accord with the σ_I and E_s values of Taft (pp. 242–245) so that only inductive and steric effects are important, and not resonance (hyperconjugative) effects.[54]

Orientation. When an unsymmetrical reagent is added to an unsymmetrical substrate, the question arises, which side of the reagent goes to which side of the double or triple bond? For electrophilic attack, the answer is given by *Markovnikov's rule: the positive portion of the reagent goes to the side of the double or triple bond which has more hydrogens.* A number of explanations have been suggested for this, but the most probable is that Y^+ adds to that side which will give the more stable carbonium ion. Thus, when an alkyl group is present, secondary carbonium ions are more stable than primary:



Markovnikov's rule also applies for halogen substituents, because the halogen stabilizes the carbonium ion by resonance:



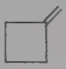
Another explanation sometimes offered for Markovnikov's rule is that the electrophile attacks the more negative position, but this is at variance with the results in certain cases. It has been shown that, for both $CH_2{=}CHCl$ and $CH_2{=}CHCF_3$, the CH_2 carbon is more negative, and yet the proton of HCl attacks the CH_2 carbon of vinyl chloride, but the $CHCF_3$ carbon of 3,3,3-trifluoropropene.[55] However, in each case the more stable carbonium ion was formed. As indicated, olefins containing the CF_3 group violate Markovnikov's rule, and this is also true for the $Me_3\overset{\oplus}{N}$ group. In the latter case attack at the Markovnikov position would give an ion with positive charges on adjacent carbons.

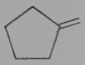
---

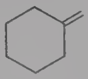
[54] Dubois and Mouvier, *Tetrahedron Letters* **1963**, 1325; Dubois and Goetz, *Tetrahedron Letters* **1965**, 303.

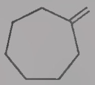
[55] Bodot and Jullien, *Bull. Soc. chim. France* **1962**, 1488.

With some compounds, anomalous results are obtained which are not easily explained by any theory. For example, allyl chloride treated with HI gives only 1-chloro-2-iodopropane, in accord with Markovnikov's rule, but with HOCl it gives 70% 2,3-dichloro-1-propanol, in violation of it.[56] When the series of alkenes **19** to **22** was treated with HOCl, **20** and **22** gave products in accord with Markovnikov's rule, while **19** and **21** gave opposite orientation.[57] This may perhaps be explained by different conformational preferences of carbonium ions with the charge on the ring, but then how do we explain the fact that, with HBr and HOBr, all four compounds gave products in accord with Markovnikov's rule?


19

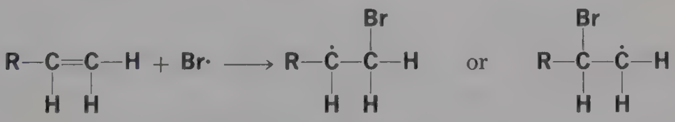

20


21


22

For nucleophilic addition the direction of attack has been studied very little, except for Michael-type addition, with compounds of the type C=C—Z. Here the negative part of the reagent *always* attacks the carbon which does not carry the Z (see p. 568).

In free-radical addition the radical attacks at that position which gives the more stable radical. This is usually the same position which would give the more stable carbonium ion, since the order of radical stability is the same as the order of carbonium-ion stability, namely, tertiary > secondary > primary. With a reagent such as HBr, this means that the addition is anti-Markovnikov, since it is Br· which is attacking:



$$\mathrm{R{-}\underset{\underset{H}{|}}{C}{=}\underset{\underset{H}{|}}{C}{-}H + Br\cdot \longrightarrow R{-}\underset{\underset{H}{|}}{\dot{C}}{-}\overset{\overset{Br}{|}}{\underset{\underset{H}{|}}{C}}{-}H} \quad \text{or} \quad \mathrm{R{-}\overset{\overset{Br}{|}}{\underset{\underset{H}{|}}{C}}{-}\underset{\underset{H}{|}}{\dot{C}}{-}H}$$

More stable

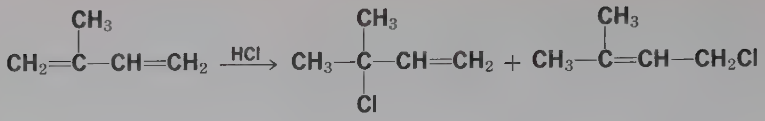
Thus, the observed orientation in both kinds of HBr addition is caused by formation of the more stable intermediate, and in each case it is the secondary intermediate which is preferred to the primary (or the tertiary to the secondary or primary). The difference in orientation results from the fact that in electrophilic addition it is H^+ which attacks, but in radical addition it is Br·. Internal olefins with no groups present to stabilize the radical usually give approximately a 1:1 mixture.

For conjugated dienes, attack by a positive ion, a negative ion, or a free radical is always at the *end* of the conjugated system, since in each case this gives an intermediate stabilized by resonance. In the case of an unsymmetrical diene, the more stable ion is the one that is formed. For example, isoprene, treated with HCl, gives only **23** and **24** with none of the product arising from attack at the other end. $PhCH{=}CHCH{=}CH_2$ gives only

---

[56] Shelton and Lee, *J. Org. Chem.* **25**, 907 (1960).

[57] Traynham and Pascual, *Tetrahedron* **7**, 165 (1959).

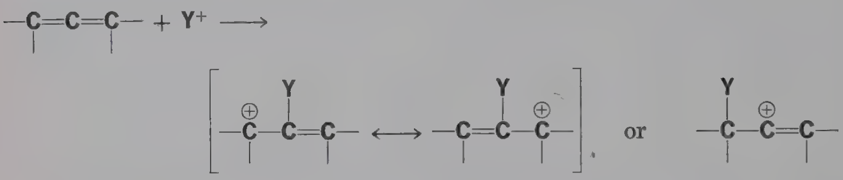


$$CH_2{=}\overset{CH_3}{\overset{|}{C}}{-}CH{=}CH_2 \xrightarrow{HCl} CH_3{-}\underset{Cl}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}{-}CH{=}CH_2 + CH_3{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}CH_2Cl$$

23 24

PhCH=CHCHClCH$_3$, since it is the only one of the eight possible products which has a double bond in conjugation with the ring and which results from attack by H$^+$ at an end of the conjugated system.

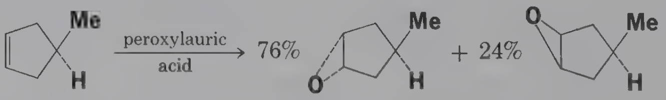
When allenes are attacked by electrophilic reagents,[57a] Markovnikov's rule would predict that the attack should be at the end of the system, since there are no hydrogens in the middle. On the other hand, attack at the center gives a carbonium ion with resonance, while attack at an end does not:



$$-\underset{|}{C}{=}C{=}\underset{|}{C}- + Y^+ \longrightarrow \left[-\underset{|}{\overset{\oplus}{C}}-\overset{Y}{\overset{|}{C}}{=}\underset{|}{C}- \longleftrightarrow -\underset{|}{C}{=}\overset{Y}{\overset{|}{C}}-\underset{|}{\overset{\oplus}{C}}-\right] \text{ or } -\underset{|}{\overset{Y}{\overset{|}{C}}}-\overset{\oplus}{C}{=}\underset{|}{C}-$$

Nevertheless, attack is most often at the end,[58] though center attack has also been reported.[59] Free radicals also attack allenes most often at the end,[60] though here too attack at the middle has been reported.[61] It has been postulated that, at least in some of these cases, attack was actually at the end, but then isomerization occurred.

Stereochemical Orientation. It has already been pointed out that some additions are cis, with both groups approaching from the same side, and that others are trans, with the groups approaching from opposite sides of the double or triple bond. For cyclic compounds there are further aspects of steric orientation. In cis addition to an unsymmetrical cyclic olefin, the two groups can come in from the more hindered side or from the less hindered side of the double bond. The rule is that cis addition is usually, though not always, from the less hindered side.[62] For example, epoxidation of 4-methylcyclopentene gave 76% addition from the less hindered and 24% from the more hindered side:[63]



[57a] For a review of addition to allenes, see Taylor, Ref. 38, pp. 338–346.

[58] See, for example, Jacobs and Johnson, *J. Am. Chem. Soc.* **82,** 6397 (1960).

[59] See Peer, *Rec. trav. chim.* **81,** 113 (1962); Fedorova, *J. Gen. Chem. USSR* **33,** 3508 (1963).

[60] Griesbaum, Oswald, Quiram, and Naegele, *J. Org. Chem.* **28,** 1952 (1963).

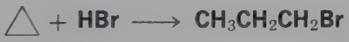
[61] van der Ploeg, Knotnerus, and Bickel, *Rec. trav. chim.* **81,** 775 (1962); Kovachic and Leitch, *Can. J. Chem.* **39,** 363 (1961); Griesbaum, Oswald, and Hall, *J. Org. Chem.* **29,** 2404 (1964); Abell and Anderson, *Tetrahedron Letters* **1964,** 3727.

[62] For a review of stereoselectivity in cyclic additions, see Henbest, *Proc. Chem. Soc.* **1963,** 159–165.

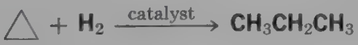
[63] Henbest and McCullough, *Proc. Chem. Soc.* **1962,** 74.

It has been mentioned that additions of Br_2 and HOBr are trans because of formation of bromonium ions and that free-radical addition of HBr is also trans, presumably because of formation of the analogous cyclic-radical intermediates. When the substrate in any of these additions is a cyclohexene, then the addition is not only trans, but the product is conformationally specific too, being mostly diaxial.[64] This is so because diaxial opening of the three-membered ring preserves in the transition state a maximum coplanarity of the participating centers; indeed, epoxides also give, on opening, diaxial products.

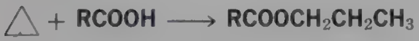
Addition to Cyclopropane Rings. In many reactions, cyclopropane rings resemble double bonds in behavior and give analogous products.[65] It may be recalled that the σ orbitals of cyclopropane rings are bent and in some respects resemble π orbitals (p. 117). Both ionic and free-radical ring-opening mechanisms have been demonstrated. The direction of ring opening of unsymmetrical cyclopropanes is similar to that for attack at double bonds. Thus methylcyclopropane, treated with HBr, gives 2-bromobutane, which is in accord with Markovnikov's rule. Examples of some ring openings, and the reaction number of the analogous addition reactions, are:



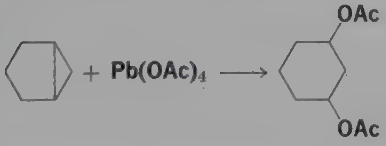
(5-1)



(5-11)

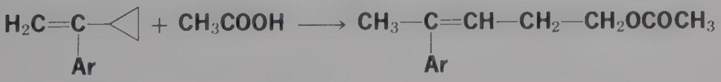


(5-6)



(5-28)[66]

In some cases conjugate addition has been performed on systems where a double bond is "conjugated" with a cyclopropyl ring. An example is[67]



(5-6)

REACTIONS

Reactions are classified by type of reagent. All reactions where hydrogen adds to one side of the double bond, whether by electrophilic, nucleophilic, free-radical, or cyclic mechanisms are treated first.

---

[64] Barton, in "Theoretical Organic Chemistry, The Kekulé Symposium," pp. 127–143, Butterworth Scientific Publications, London, 1959; Goering, Abell, and Aycock, *J. Am. Chem. Soc.* **74,** 3588 (1952); Goering and Sims, *J. Am. Chem. Soc.* **77,** 3465 (1955); Shoppee, Akhtar, and Lack, *J. Chem. Soc.* **1964,** 877; Readio and Skell, *J. Org. Chem.* **31,** 753, 759 (1966).

[65] For a review, see Lukina, *Russ. Chem. Rev.* **31,** 419 (1962). The analogies are by no means complete: see Gordon, *J. Chem. Educ.* **44,** 461 (1967).

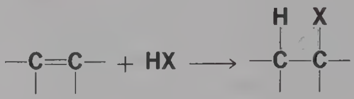
[66] Moon, *J. Org. Chem.* **29,** 3456 (1964).

[67] Sarel and Ben-Shoshan, *Tetrahedron Letters* **1965,** 1053.

Reactions in Which Hydrogen Adds to One Side

A. Halogen on the other side

5-1 Addition of hydrogen halides

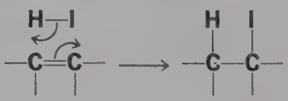


$$-\overset{|}{\underset{|}{C}}=\underset{|}{C}- + HX \longrightarrow -\overset{H}{\underset{|}{\overset{|}{C}}}-\overset{X}{\underset{|}{\overset{|}{C}}}-$$

Any of the four hydrogen halides may be added to double bonds. HI, HBr, and HF[68] add at room temperature. The addition of HCl usually requires heat. The reaction can be carried out with a large variety of double-bond compounds, including conjugated systems, where both 1,2 and 1,4 addition are possible. It is also possible to add one or two moles of any of the four hydrogen halides to triple bonds.

The addition of hydrogen halides to simple olefins, in the absence of peroxides, takes place by an electrophilic mechanism, and the orientation is in accord with Markovnikov's rule.[69] When peroxides are added, the addition of HBr occurs by a free-radical mechanism, and the orientation is anti-Markovnikov (p. 577).[70] It must be emphasized that this is true only for HBr. Free-radical addition of HF and HI has never been observed, even in the presence of peroxides, and of HCl, only rarely. In the rare cases where free-radical addition of HCl was noted, the orientation was still Markovnikov, presumably because the more stable *product* was formed.[71] Free-radical addition of HF, HI, and HCl is energetically unfavorable.

HX are electrophilic reagents, and many polyhalo and polycyano halides (for example, $Cl_2C{=}CHCl$) do not react with them at all, in the absence of free-radical conditions. When such reactions do occur, however, they take place by a nucleophilic addition mechanism; that is, initial attack is by X^-. This type of mechanism also occurs with Michael-type substrates C=C—Z, where the orientation is always such that the halogen goes to the carbon which does not bear the Z, so that the product is of the form X—C—CH—Z, even in the presence of free-radical initiators. HI adds to ordinary olefins in the gas phase, where the mechanism is likely a four-center one:



Markovnikov's rule is followed in these additions.[72] However, the alkyl iodide formed may be reduced by excess HI: RI + HI ⟶ RH. If this is desired, then the overall process becomes a way of hydrogenating a double bond.[73]

---

[68] For a review of addition of HF, see Wiechert, in "Newer Methods of Preparative Organic Chemistry," vol. 1, pp. 315–368, Interscience Publishers, Inc., New York, 1948.

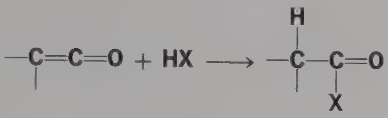
[69] For a review of electrophilic addition of HX, see Dewar, *Angew. Chem. Intern. Ed. Engl.* **3,** 245–249 (1964).

[70] For reviews of free-radical addition of HX, see Stacey and Harris, *Org. Reactions* **13,** 150–376 (1963), pp. 154–164, 238–246; Sosnovsky, Ref. 26, pp. 6–18; Walling, Ref. 26, pp. 291–298.

[71] Mayo, *J. Am. Chem. Soc.* **84,** 3964 (1962).

[72] Bose and Benson, *J. Chem. Phys.* **37,** 1081 (1962).

HX may be added to ketenes to give acyl halides:

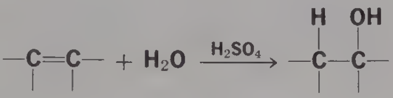


$$-\underset{|}{C}{=}C{=}O + HX \longrightarrow -\overset{\overset{H}{|}}{\underset{|}{C}}-\underset{\underset{X}{|}}{C}{=}O$$

OS **I,** 166; **II,** 137, 336; **III,** 576; **IV,** 238, 543.

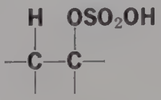
B. Oxygen on the other side

5-2 Hydration of olefins



$$-\underset{|}{C}{=}\underset{|}{C}- + H_2O \xrightarrow{H_2SO_4} -\overset{\overset{H}{|}}{\underset{|}{C}}-\overset{\overset{OH}{|}}{\underset{|}{C}}-$$

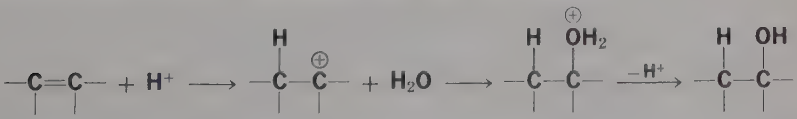
Olefins can be hydrated by treatment with water and an acid catalyst. The most common catalyst is sulfuric acid, but other acids, such as nitric, may also be used. The mechanism is electrophilic and begins with attack by a proton. The negative attacking species may be HSO_4^- (or similar ion in the case of other acids) to give the initial product



$$-\overset{\overset{H}{|}}{\underset{|}{C}}-\overset{\overset{OSO_2OH}{|}}{\underset{|}{C}}-$$

25

which may be isolated (reaction **5-4**) but, under the conditions of the reaction, is usually hydrolyzed to the alcohol (reaction **0-4,** p. 305). However, the conjugate base of the acid is not the only possible species which attacks the initial carbonium ion. The attack may also be by water:



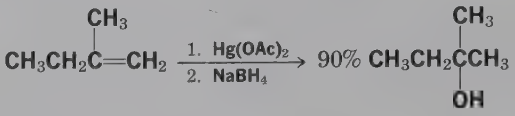
$$-\underset{|}{C}{=}\underset{|}{C}- + H^+ \longrightarrow -\overset{\overset{H}{|}}{\underset{|}{C}}-\overset{\oplus}{\underset{|}{C}}- + H_2O \longrightarrow -\overset{\overset{H}{|}}{\underset{|}{C}}-\overset{\overset{\overset{\oplus}{OH_2}}{|}}{\underset{|}{C}}- \xrightarrow{-H^+} -\overset{\overset{H}{|}}{\underset{|}{C}}-\overset{\overset{OH}{|}}{\underset{|}{C}}-$$

When the reaction proceeds by this pathway, then **25** and similar intermediates are not involved, and the mechanism is exactly the reverse of E1 elimination of alcohols (reaction **7-1,** p. 753). It is likely that the mechanism involves both pathways. Sometimes the initial carbonium ion rearranges to a more stable one. For example, hydration of $CH_2{=}CHCH(CH_3)_2$ gives $CH_3CH_2COH(CH_3)_2$. With ordinary olefins the addition predominantly follows Markovnikov's rule. For a method of anti-Markovnikov hydration, see reaction **5-13.** With substrates of the type C═C—Z (Z is as defined on p. 568) the product is always HO—C—CH—Z, and the mechanism is nucleophilic. Conjugated dienes are seldom hydrated.

---

[73] Benson and Bose, *J. Chem. Phys.* **37,** 2935 (1962), **38,** 878 (1963).

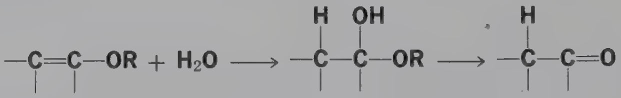
Olefins can be hydrated quickly, under mild conditions in high yields without rearrangement products, by the use of oxymercuration (addition of oxygen and mercury) followed by *in situ* treatment with sodium borohydride.[73a] For example, 2-methyl-1-butene, treated with mercuric acetate, followed by $NaBH_4$, gave 90% 2-methyl-2-butanol



$$CH_3CH_2\overset{CH_3}{\overset{|}{C}}{=}CH_2 \xrightarrow[\text{2. } NaBH_4]{\text{1. } Hg(OAc)_2} 90\%\ CH_3CH_2\underset{OH}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}CH_3$$

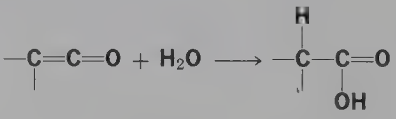
This method gives almost complete Markovnikov addition.

Addition of water to vinyl ethers gives hemiacetals, which spontaneously form aldehydes:



$$-\underset{|}{C}{=}\underset{|}{C}-OR + H_2O \longrightarrow -\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{|}{\overset{OH}{\overset{|}{C}}}-OR \longrightarrow -\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{|}{C}{=}O$$

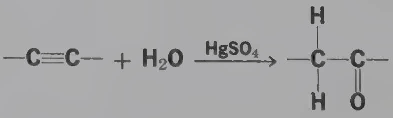
Ketenes add water spontaneously to give carboxylic acids:



$$-\underset{|}{C}{=}C{=}O + H_2O \longrightarrow -\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{OH}{\underset{|}{C}}{=}O$$

OS **IV,** 555, 560. Also see OS **40,** 76.

5-3 Hydration of alkynes



$$-C{\equiv}C- + H_2O \xrightarrow{HgSO_4} -\underset{H}{\underset{|}{\overset{H}{\overset{|}{C}}}}-\underset{O}{\underset{\|}{C}}-$$

Alkynes may be hydrated with mercuric sulfate as catalyst.[74] Since the addition follows Markovnikov's rule, only acetylene gives an aldehyde. All other triple-bond compounds give ketones. With alkynes of the form RC≡CH methyl ketones are formed almost exclusively, but with RC≡CR′ both possible products are usually obtained. However, if R is primary and

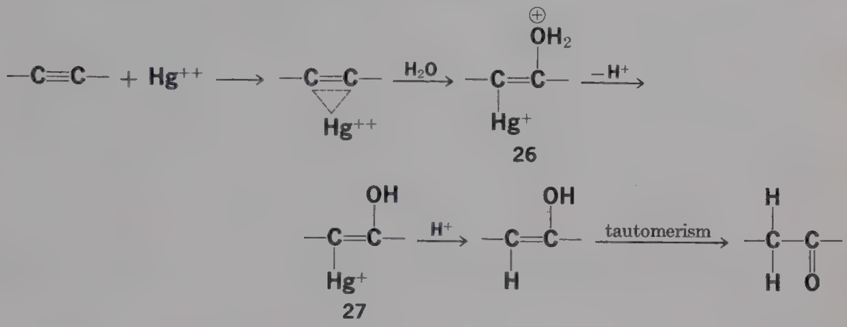
---

[73a] Brown and Geoghegan, *J. Am. Chem. Soc.* **89,** 1522 (1967); Brown and Hammar, *J. Am. Chem. Soc.* **89,** 1524 (1967); Brown, Kawakami, and Ikegami, *J. Am. Chem. Soc.* **89,** 1525 (1967). For reviews of oxymercuration, see Zefirov, *Russ. Chem. Rev.* **34,** 527–536 (1965); and Chatt, *Chem. Rev.* **48,** 7–43 (1951).

[74] For a review, see Miocque, Hung, and Yen, *Ann. chim.* (*Paris*) [13] **8,** 157–174 (1963).

R′ secondary or tertiary, the carbonyl group is formed preferentially next to the secondary or tertiary carbon.[75]

The first step of the mechanism is probably formation of a complex, since ions like Hg^{++} form complexes with alkynes (p. 66). Water then attacks in an S_N2-type process to give the intermediate **26**:

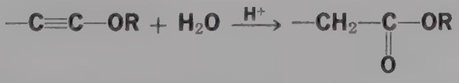


26

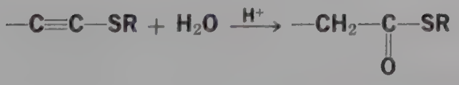
27

which loses a proton to give **27**. Hydrolysis of **27** (an example of reaction **2-14**, p. 470) gives the enol, which tautomerizes to the product.[76] There is evidence that the mechanism is somewhat more complicated than this. A yellow color has been observed in the solution which, from spectral evidence, is attributed to a complex containing an Hg^{++} ion and *two* acetylene molecules.[77] The isolation of **26** or **27** would be strong evidence in favor of the above mechanism. Such intermediates have not been isolated, but an analogous intermediate has been isolated from treatment of olefins with mercuric salts.

Alkynes may also be hydrated in the vapor phase with other catalysts (e.g., copper, cadmium, zinc salts).[78] Esters and thiol esters can be made by acid-catalyzed hydration of, respectively, acetylenic ethers and thioethers, without a mercuric catalyst:[79]



$$-C\equiv C-OR + H_2O \xrightarrow{H^+} -CH_2-\underset{\underset{\displaystyle O}{\|}}{C}-OR$$



$$-C\equiv C-SR + H_2O \xrightarrow{H^+} -CH_2-\underset{\underset{\displaystyle O}{\|}}{C}-SR$$

This is ordinary electrophilic addition, with rate-determining protonation as the first step.[80] Certain other alkynes have also been hydrated to ketones

[75] Krupin and Petrov, *J. Gen. Chem. USSR* **33,** 3799 (1963).

[76] Rochow, Hurd, and Lewis, "The Chemistry of Organometallic Compounds," pp. 109–112, John Wiley & Sons, Inc., New York, 1957.

[77] Budde and Dessy, *Tetrahedron Letters* **1963,** 651, *J. Am. Chem. Soc.* **85,** 3964 (1963).

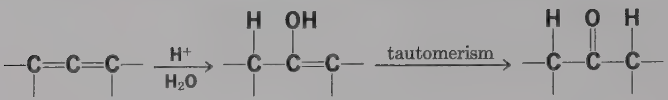
[78] Gorn and Gorin, *J. Gen. Chem. USSR* **29,** 2090 (1959).

[79] Arens, *Advan. Org. Chem.* **2,** 163 (1960).

[80] Hogeveen and Drenth, *Rec. trav. chim.* **82,** 375, 410 (1963); Stamhuis and Drenth, *Rec. trav. chim.* **82,** 385, 394 (1963).

with strong acids in the absence of mercuric salts. These include ArC≡CCOOH[81] and 3-hexyne.[82]

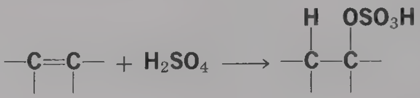
Allenes may also be hydrolyzed to ketones, with an acid catalyst:[83]



$$-\overset{|}{C}=C=\underset{|}{C}- \xrightarrow[H_2O]{H^+} -\underset{|}{\overset{H}{C}}-\overset{OH}{C}=\underset{|}{C}- \xrightarrow{\text{tautomerism}} -\underset{|}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-\underset{|}{\overset{H}{C}}-$$

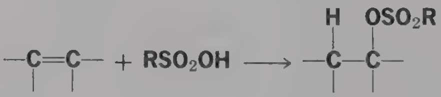
OS **III**, 22; **IV**, 13; **40**, 88.

5-4 Formation of inorganic esters



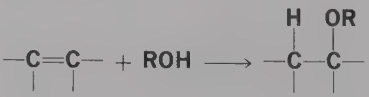
$$-\underset{|}{C}=\underset{|}{C}- + H_2SO_4 \longrightarrow -\underset{|}{\overset{H}{C}}-\underset{|}{\overset{OSO_3H}{C}}-$$

It is possible to prepare esters of sulfuric acid by treatment of olefins with H_2SO_4, but care must be taken that the esters do not hydrolyze to the alcohol (reaction **5-2**). It is also possible for the product to add to a second molecule of olefin to give a dialkyl sulfate. In practice, however, the reaction is seldom used for any olefin except ethylene. Esters of inorganic acids are most often prepared from alcohols (reaction **0-32**, p. 326). Sulfonic acids add to many olefins, though not to ethylene, to give sulfonic esters:



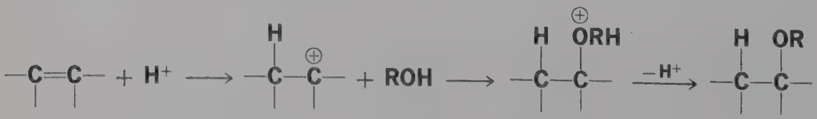
$$-\underset{|}{C}=\underset{|}{C}- + RSO_2OH \longrightarrow -\underset{|}{\overset{H}{C}}-\underset{|}{\overset{OSO_2R}{C}}-$$

5-5 Addition of alcohols and phenols



$$-\underset{|}{C}=\underset{|}{C}- + ROH \longrightarrow -\underset{|}{\overset{H}{C}}-\underset{|}{\overset{OR}{C}}-$$

Alcohols and phenols add to olefins in reactions which are catalyzed by acids or bases. When the reactions are acid-catalyzed, the mechanism is electrophilic, with H^+ as the attacking species. The resulting carbonium ion combines with a molecule of alcohol:



$$-\underset{|}{C}=\underset{|}{C}- + H^+ \longrightarrow -\underset{|}{\overset{H}{C}}-\underset{|}{\overset{\oplus}{C}}- + ROH \longrightarrow -\underset{|}{\overset{H}{C}}-\underset{|}{\overset{\overset{\oplus}{O}RH}{C}}- \xrightarrow{-H^+} -\underset{|}{\overset{H}{C}}-\underset{|}{\overset{OR}{C}}-$$

---

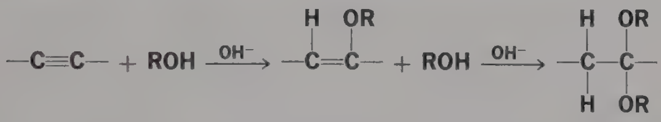
[81] Noyce, Matesich, Schiavelli, and Peterson, *J. Am. Chem. Soc.* **87**, 2295 (1965).

[82] Richey and Buckley, cited by Deno, *Progr. Phys. Org. Chem.* **2**, 181 (1964).

[83] For example, see Fedorova and Petrov, *J. Gen. Chem. USSR* **32**, 1740 (1962).

The addition, therefore, follows Markovnikov's rule. Primary alcohols give better results than secondary, and tertiary alcohols are very inactive. This is a convenient method for the preparation of tertiary ethers, by the use of a suitable olefin such as $Me_2C{=}CH_2$.

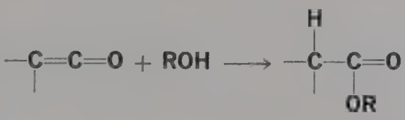
For those substrates which are more susceptible to nucleophilic attack (e.g., polyhalo olefins and olefins of the type $C{=}C{-}Z$), it is better to carry out the reaction in basic solution, where the attacking species is RO^-.[84] The reactions with $C{=}C{-}Z$ are of the Michael type, and OR always goes to the side away from the Z.[85] Since triple bonds are more susceptible to nucleophilic attack than are double bonds, it might be expected that bases would catalyze addition to triple bonds particularly well. This is the case, and vinyl ethers and acetals may be produced by this reaction:[86]



$$-\text{C}\equiv\text{C}- + \text{ROH} \xrightarrow{\text{OH}^-} -\overset{\text{H}}{\overset{|}{\text{C}}}=\overset{\text{OR}}{\overset{|}{\text{C}}}- + \text{ROH} \xrightarrow{\text{OH}^-} -\underset{\text{H}}{\underset{|}{\overset{\text{H}}{\overset{|}{\text{C}}}}}-\underset{\text{OR}}{\underset{|}{\overset{\text{OR}}{\overset{|}{\text{C}}}}}-$$

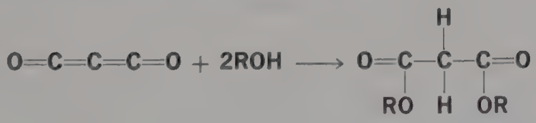
In base-catalyzed addition to triple bonds the rate falls in going from a primary to a tertiary alcohol, and phenols require more severe conditions. Other catalysts, namely, BF_3 and mercuric salts, have also been used in addition of ROH to triple bonds.

Both alcohols and phenols add to ketenes to give esters:[87]



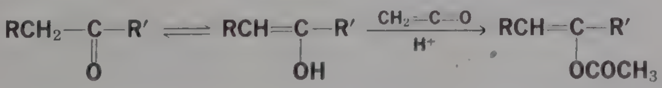
$$-\underset{|}{\text{C}}=\text{C}=\text{O} + \text{ROH} \longrightarrow -\underset{|}{\overset{\text{H}}{\overset{|}{\text{C}}}}-\underset{\text{OR}}{\underset{|}{\text{C}}}=\text{O}$$

Similarly, carbon suboxide gives malonic esters:



$$\text{O}=\text{C}=\text{C}=\text{C}=\text{O} + 2\text{ROH} \longrightarrow \text{O}=\underset{\text{RO}}{\underset{|}{\text{C}}}-\underset{\text{H}}{\underset{|}{\overset{\text{H}}{\overset{|}{\text{C}}}}}-\underset{\text{OR}}{\underset{|}{\text{C}}}=\text{O}$$

In the presence of a strong acid, ketene reacts with aldehydes or ketones (in their enol forms) to give enol acetates:



$$\text{RCH}_2-\underset{\text{O}}{\underset{\|}{\text{C}}}-\text{R}' \rightleftharpoons \text{RCH}=\underset{\text{OH}}{\underset{|}{\text{C}}}-\text{R}' \xrightarrow[\text{H}^+]{\text{CH}_2=\text{C}=\text{O}} \text{RCH}=\underset{\text{OCOCH}_3}{\underset{|}{\text{C}}}-\text{R}'$$

---

[84] See, for example, Lichtenberger and Rusch, *Bull. Soc. chim. France* **1962**, 254, 325.

[85] For a review of addition of ROH to acrylonitrile (cyanoethylation of alcohols and phenols), see Bruson, *Org. Reactions* **5**, 79–135 (1949), pp. 89–95, 121–128.

[86] For a review, see Shostakovskii, Bogdanova, and Plotnikova, *Russ. Chem. Rev.* **33**, 66–77 (1964).

[87] Lacey, *Advan. Org. Chem.* **2**, 213–263 (1960), pp. 216–217; Quadbeck, in Foerst, "Newer Methods of Preparative Organic Chemistry," vol. 2, pp. 133–161, Academic Press Inc., New York, 1963; this article also appeared in *Angew. Chem.* **68**, 361 (1956).

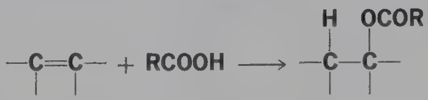
The hydroxy group of oximes also adds to those substrates susceptible to nucleophilic attack, e.g.,[85,41]

$$\mathrm{Me_2C{=}NOH + CH_2{=}CH{-}CN \longrightarrow Me_2C{=}NOCH_2CH_2CN}$$

$$\mathrm{Me_2C{=}NOH + F_2C{=}CF_2 \longrightarrow Me_2C{=}NOCF_2CF_2H}$$

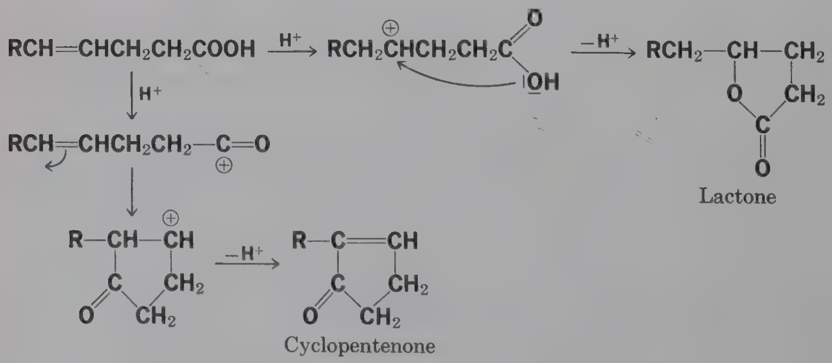
Alcohols can also add to olefins in a different way (see reaction **5-16**).
OS **III**, 371; **IV**, 184, 558.

5-6 Addition of carboxylic acids



$$-\overset{|}{\underset{|}{C}}{=}\overset{|}{\underset{|}{C}}- + \mathrm{RCOOH} \longrightarrow -\overset{\mathrm{H}}{\underset{|}{\overset{|}{C}}}-\overset{\mathrm{OCOR}}{\underset{|}{\overset{|}{C}}}-$$

Esters are produced by the addition of carboxylic acids to olefins, a reaction which is usually acid-catalyzed and similar in mechanism to reaction **5-5.** Since Markovnikov's rule is followed, hard-to-get esters of tertiary alcohols may be prepared by addition to olefins of the form $R_2C{=}CHR$.[88] When a carboxylic acid which contains a double bond in the chain is treated with a strong acid, then the addition occurs internally, and the product is a γ- and/or a δ-lactone, regardless of the original position of the double bond in the chain, since strong acids catalyze double-bond shifts (reaction **2-2**, p. 453).[89] The double bond always migrates to a position favorable for the reaction, whether this has to be toward or away from the carboxyl group. However, another reaction competes, in which the product is a cyclopentenone or a cyclohexenone. This is essentially an example of reaction **2-9** (p. 463). In either case, first the double bond migrates into the proper position, and then a proton from the catalyst may attack the acid in two ways. It either adds to the double bond or removes OH^- from the carboxyl group, leaving an acylonium ion:



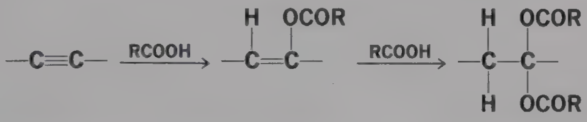
---

[88] See, for example, Peterson and Tao, *J. Org. Chem.* **29**, 2322 (1964).

[89] For a review of such lactonizations, see Ansell and Palmer, *Quart. Rev.* (*London*) **18**, 211–225 (1964).

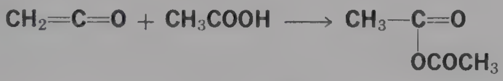
If it adds to the double bond, normal lactonization occurs, but if it creates an acylonium ion, *this* attacks the double bond and the ketone product is formed. Actually, the fact that trans addition is observed in the lactonization indicates that the two steps of this process are probably concerted or nearly so. Which type of reaction is predominant depends mainly on which type of acid is used as catalyst. Proton-donating acids, for example, H_2SO_4, HCOOH, HF, give mostly lactones, while Lewis acids like acetic anhydride, $ZnCl_2$ in HOAc, P_2O_5, etc., are among those which give mostly ketones. Since carbonium ions are involved, rearrangements take place in both reactions.

Triple bonds may give alkenyl esters or acylals when treated with carboxylic acids. Mercuric salts are usually catalysts:



$$-C\equiv C- \xrightarrow{RCOOH} -\overset{H}{C}=\overset{OCOR}{C}- \xrightarrow{RCOOH} -\underset{H}{\overset{H}{C}}-\underset{OCOR}{\overset{OCOR}{C}}-$$

With ketenes, carboxylic acids give anhydrides, and acetic anhydride is prepared industrially in this manner:



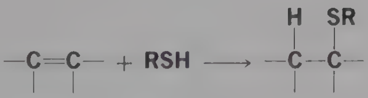
$$CH_2=C=O + CH_3COOH \longrightarrow CH_3-\underset{OCOCH_3}{C}=O$$

Esters may also be obtained by the addition to olefins of acyl peroxides.[90] These reactions are catalyzed by copper and are free-radical processes.

OS **III,** 853; **IV,** 261, 417, 444; **42,** 79; **45,** 74. Also see OS **I,** 317.

C. Sulfur on the other side

5-7 Addition of H_2S and mercaptans



$$-\underset{|}{C}=\underset{|}{C}- + RSH \longrightarrow -\underset{|}{\overset{H}{C}}-\underset{|}{\overset{SR}{C}}-$$

H_2S and mercaptans may add to olefins by electrophilic, nucleophilic, or free-radical mechanisms.[91] In the absence of initiators the addition to simple olefins is by an electrophilic mechanism, similar to that in reaction **5-5,** and Markovnikov's rule is followed. However, this reaction is usually very slow and often cannot be done or requires very severe conditions, unless an acid catalyst is used. For example, the reaction may be performed in concentrated H_2SO_4.[92] In the presence of free-radical initiators, H_2S and mercaptans add to double and triple bonds by a free-radical mechanism, and the orientation is anti-Markovnikov.[93] In fact the orientation may be used as a diagnostic tool to indicate which mechanism is operating. Free-radical addition may be done with H_2S, RSH (R may be primary, secondary, or tertiary), ArSH, RCOSH, and even $(RO)_2PSSH$. R may contain various functional groups. The olefin may be terminal, internal, contain branching, be cyclic, and have various functional groups including OH, COOH, COOR, NO_2, RSO_2, etc. With acetylenes it is possible to add one or two moles of RSH.

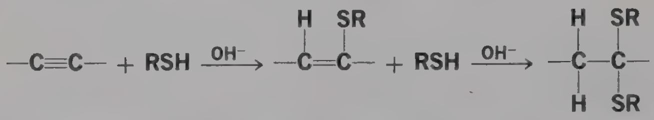
---

[90] Kharasch and Fono, *J. Org. Chem.* **24,** 606 (1959); Kochi, *J. Am. Chem. Soc.* **84,** 1572 (1962).

[91] For a review, see Prilezhaeva and Shostakovskii, *Russ. Chem. Rev.* **32,** 399–426 (1963).

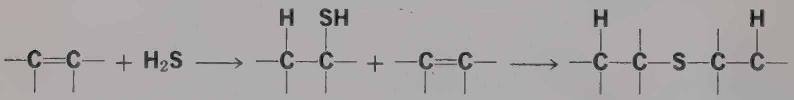
[92] Shostakovskii, Kul'bovskaya, Gracheva, Laba, and Yakushina, *J. Gen. Chem. USSR* **32,** 707 (1962).

When mercaptans are added to substrates susceptible to nucleophilic attack, then bases catalyze the reaction, and the mechanism is nucleophilic. These substrates may be of the Michael type[94] or may be polyhalo olefins or alkynes.[86] As with the free-radical mechanism, alkynes may give either vinyl thioethers or thioacetals:



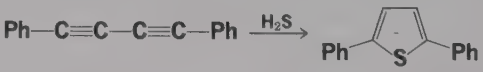
$$-\mathrm{C}\equiv\mathrm{C}- + \mathrm{RSH} \xrightarrow{\mathrm{OH^-}} -\overset{\mathrm{H}}{\mathrm{C}}=\overset{\mathrm{SR}}{\mathrm{C}}- + \mathrm{RSH} \xrightarrow{\mathrm{OH^-}} -\underset{\mathrm{H}}{\overset{\mathrm{H}}{\mathrm{C}}}-\underset{\mathrm{SR}}{\overset{\mathrm{SR}}{\mathrm{C}}}-$$

By any mechanism, the initial product of addition of H_2S to a double bond is a mercaptan, which is capable of adding to a second molecule of olefin, so that sulfides are often produced:

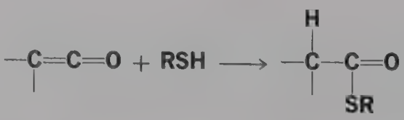


$$-\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}- + \mathrm{H_2S} \longrightarrow -\underset{|}{\overset{\mathrm{H}}{\mathrm{C}}}-\underset{|}{\overset{\mathrm{SH}}{\mathrm{C}}}- + -\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}- \longrightarrow -\underset{|}{\overset{\mathrm{H}}{\mathrm{C}}}-\underset{|}{\overset{|}{\mathrm{C}}}-\mathrm{S}-\underset{|}{\overset{|}{\mathrm{C}}}-\overset{\mathrm{H}}{\mathrm{C}}-$$

Additions to conjugated dienes have been rare. For electrophilic (acid-catalyzed) conditions, 1,4 addition has been reported.[95] For free-radical addition, both 1,2[95] and 1,4 addition[96] have been demonstrated. Conjugated diynes, treated with H_2S, give thiophenes:[97]



Conjugated triynes and tetraynes also give thiophenes. Ketenes add mercaptans to give thiol esters:



$$-\underset{|}{\mathrm{C}}=\mathrm{C}=\mathrm{O} + \mathrm{RSH} \longrightarrow -\underset{|}{\overset{\mathrm{H}}{\mathrm{C}}}-\underset{\mathrm{SR}}{\mathrm{C}}=\mathrm{O}$$

---

[93] For reviews of free-radical addition of H_2S and RSH, see Stacey and Harris, *Org. Reactions* **13**, 150–376 (1963), pp. 165–196, 247–324; Sosnovsky, Ref. 26, pp. 62–97; Walling, Ref. 26, pp. 313–326.

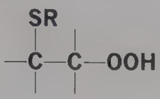
[94] For a review of additions to acrylonitrile, see Bruson, *Org. Reactions* **5**, 79–135 (1949), pp. 95–97, 129–130.

[95] Saville, *J. Chem. Soc.* **1962**, 5040.

[96] Oswald, Griesbaum, Thaler, and Hudson, *J. Am. Chem. Soc.* **84**, 3897 (1962); Claisse and Davies, *J. Chem. Soc.* **1965**, 4894, obtained both 1,2 and 1,4 products.

[97] Schulte, Reisch, and Hörner, *Chem. Ber.* **95**, 1943 (1962).

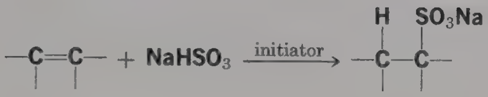
When mercaptans add to olefins by a free-radical mechanism in the presence of oxygen, then β-hydroperoxy sulfides are side products:



$$-\overset{\text{SR}}{\underset{|}{\overset{|}{\text{C}}}}-\underset{|}{\overset{|}{\text{C}}}-\text{OOH}$$

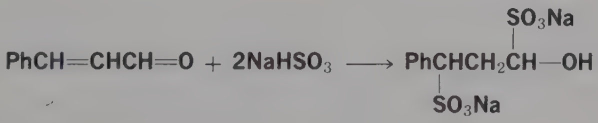
OS **III**, 458; **IV**, 669.

5-8 Addition of sodium bisulfite



$$-\underset{|}{\text{C}}=\underset{|}{\text{C}}- + \text{NaHSO}_3 \xrightarrow{\text{initiator}} -\overset{\text{H}}{\underset{|}{\overset{|}{\text{C}}}}-\overset{\text{SO}_3\text{Na}}{\underset{|}{\overset{|}{\text{C}}}}-$$

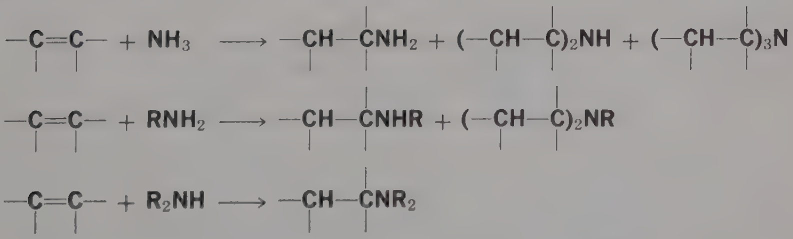
Salts of aliphatic sulfonic acids may be prepared by addition of bisulfite salts to olefins in the presence of free-radical initiators.[97a] The orientation is anti-Markovnikov. On systems of the type C=C—C=O, bis addition may be observed:



$$\text{PhCH}{=}\text{CHCH}{=}\text{O} + 2\text{NaHSO}_3 \longrightarrow \text{Ph}\underset{\text{SO}_3\text{Na}}{\underset{|}{\text{C}}}\text{HCH}_2\overset{\text{SO}_3\text{Na}}{\overset{|}{\text{C}}}\text{H}-\text{OH}$$

D. Nitrogen on the other side

5-9 Addition of ammonia and amines



$$-\underset{|}{\text{C}}=\underset{|}{\text{C}}- + \text{NH}_3 \longrightarrow -\underset{|}{\text{C}}\text{H}-\underset{|}{\overset{|}{\text{C}}}\text{NH}_2 + (-\underset{|}{\text{C}}\text{H}-\underset{|}{\overset{|}{\text{C}}})_2\text{NH} + (-\underset{|}{\text{C}}\text{H}-\underset{|}{\overset{|}{\text{C}}})_3\text{N}$$

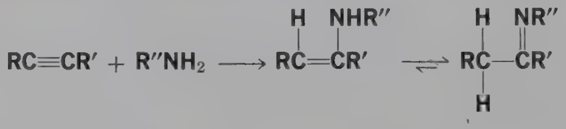
$$-\underset{|}{\text{C}}=\underset{|}{\text{C}}- + \text{RNH}_2 \longrightarrow -\underset{|}{\text{C}}\text{H}-\underset{|}{\overset{|}{\text{C}}}\text{NHR} + (-\underset{|}{\text{C}}\text{H}-\underset{|}{\overset{|}{\text{C}}})_2\text{NR}$$

$$-\underset{|}{\text{C}}=\underset{|}{\text{C}}- + \text{R}_2\text{NH} \longrightarrow -\underset{|}{\text{C}}\text{H}-\underset{|}{\overset{|}{\text{C}}}\text{NR}_2$$

Ammonia, primary, and secondary amines add to olefins which are susceptible to nucleophilic attack. Ammonia gives three possible products, since the initial product is a primary amine, which may add to a second molecule of olefin, etc. Similarly, primary amines give both secondary and tertiary products. In practice it is usually possible to control which product predominates. Since ammonia and amines are much weaker acids than water, alcohols, and mercaptans (see reactions **5-2**, **5-5**, **5-7**) and since acids could hardly catalyze the reaction (because they would turn NH_3 into NH_4^+), this reaction does not occur by an electrophilic mechanism and so gives very low yields, if any, with ordinary olefins. The mechanism is nearly always nucleophilic, and the reaction is generally performed on polyhalo olefins, Michael-type substrates, and alkynes. As expected, on Michael-type substrates the nitrogen goes to the carbon which does not carry the Z.[98] Other nitrogenous compounds, among them hydroxylamine, hydrazines, amides ($RCONH_2$ and $RCONHR'$ including imides and lactams), and sulfonamides, also add to olefins. In the case of amides, basic catalysts are required, since amides are not good enough nucleophiles for the reaction, and they must be converted to $RCONH^-$. Even with amines, basic catalysts are sometimes used, so that RNH^- or R_2N^- is the actual nucleophile.

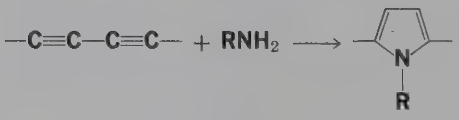
[97a] For a review, see Gilbert, "Sulfonation and Related Reactions," pp. 148–156, Interscience Publishers, Inc., New York, 1965.

Triple bonds are readily attacked.[98a] Primary amines add to give enamines, which have a hydrogen on the nitrogen and (analogously to enols) tautomerize to the more stable imines:



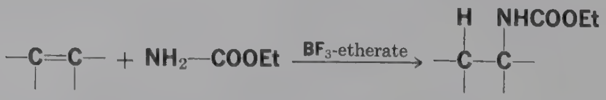
$$RC\equiv CR' + R''NH_2 \longrightarrow R\overset{H}{\overset{|}{C}}=\overset{NHR''}{\overset{|}{C}}R' \rightleftharpoons R\underset{\underset{H}{|}}{\overset{H}{\overset{|}{C}}}-\overset{NR''}{\overset{\|}{C}}R'$$

These are often stable enough for isolation.[99] When ammonia is used instead of a primary amine, the corresponding $RCH_2-\overset{NH}{\overset{\|}{C}}R'$ is not stable enough for isolation, but polymerizes. Secondary amines give enamines $RCH=CR'NR''_2$, which, lacking a hydrogen on the nitrogen, are quite stable. It has been shown that triple bonds are more susceptible than even activated double bonds to attack by amines. Thus diethylamine added to the triple bonds of *both* $CH_3COCH=CHC\equiv CH$ and $CH_3COC\equiv CCH=CH_2$.[100] Ammonia and primary amines (aliphatic and aromatic) add to conjugated diynes to give pyrroles:[101]



This is not 1,4 addition, but 1,2 addition twice.

Carbamates add to olefins and conjugated dienes (which give 1,4 addition) in the presence of BF_3-etherate to give N-substituted urethanes:[102]



$$-\underset{|}{C}=\underset{|}{C}- + NH_2-COOEt \xrightarrow{BF_3\text{-etherate}} -\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{|}{\overset{NHCOOEt}{\overset{|}{C}}}-$$

---

[98] For a review of cyanoethylation of ammonia and amines, see Bruson, *Org. Reactions* **5**, 79–135 (1949), pp. 79–89, 113–120.

[98a] For a review of addition of ammonia and amines to triple bonds, see Chekulaeva and Kondrat'eva, *Russ. Chem. Rev.* **34**, 669–680 (1965).

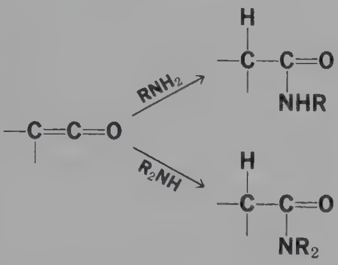
[99] For example, see Kruse and Kleinschmidt, *J. Am. Chem. Soc.* **83**, 213, 216 (1961).

[100] Bowden, Braude, Jones, and Weedon, *J. Chem. Soc.* **1946**, 45.

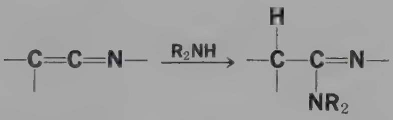
[101] Schulte, Reisch, and Walker, *Chem. Ber.* **98**, 98 (1965).

[102] Müller and Merten, *Chem. Ber.* **98**, 1097 (1965).

Primary and secondary amines add to ketenes, to give, respectively, N-substituted and N,N-disubstituted amides:



and to ketenimines to give amidines:[103]

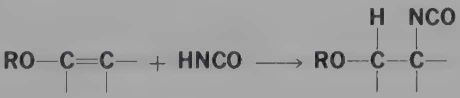


$$-\underset{|}{C}=C=N- \xrightarrow{R_2NH} -\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{\underset{NR_2}{|}}{C}=N- \qquad R = H \text{ or alkyl}$$

An indirect way of adding NH_3 to double bonds (even to ordinary double bonds) is to treat the hydroboration product of an olefin (reaction **5-13**) with NH_2Cl or hydroxylamine-O-sulfonic acid. This produces the primary amine with, of course, anti-Markovnikov orientation. The substitution is electrophilic and proceeds with retention of configuration.[104]

OS **I**, 196; **III**, 91, 93, 244, 258; **IV**, 146, 205; **43**, 45.

5-10 Addition of HNCO to vinyl ethers

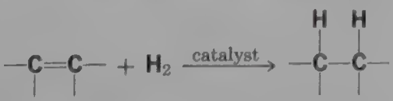


$$RO-\underset{|}{C}=\underset{|}{C}- + HNCO \longrightarrow RO-\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{|}{\overset{NCO}{\overset{|}{C}}}-$$

β-Alkoxyisocyanates may be prepared by addition of cyanic acid to vinyl ethers.[105] The orientation is always as shown.

E. Hydrogen on both sides

5-11 Hydrogenation of double and triple bonds



$$-\underset{|}{C}=\underset{|}{C}- + H_2 \xrightarrow{\text{catalyst}} -\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{|}{\overset{H}{\overset{|}{C}}}-$$

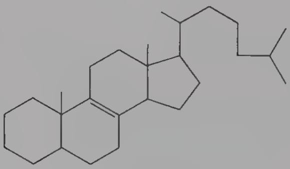
Most carbon-carbon double bonds, whether substituted by electron-donating or electron-withdrawing substituents, can be catalytically hydrogenated, usually in quantitative or near-quantitative yields.[106] According to the review of Adkins and Shriner, over 99% of all known alkenes add hydrogen at temperatures between 0 and 275°. Many functional groups may be present in the molecule, for example, OH, COOH, NH_2, CHO, COR, COOR, CN, etc. Some of these groups are also susceptible to catalytic reduction, but it is usually possible to find conditions under which double bonds can be reduced selectively. Many catalysts have been used, mostly transition metals and their compounds. Among the most effective are Raney nickel,[107] PtO_2, rhodium, ruthenium, palladium-on-charcoal, and copper chromite.[108] Hydrogenations in most cases are carried out at room temperature and just above atmospheric pressure, but some double bonds are more resistant and require higher temperatures and pressures. The resistance is usually a function of increasing substitution and is presumably caused by steric factors. Trisubstituted double bonds require, say, 25° and 100 atm, while tetrasubstituted double bonds may require 275° and 100 atm. Among the double bonds which are most difficult to hydrogenate, or which cannot be hydrogenated at all, are those common to two rings, as in **28**. Hydrogenations, even at about atmospheric pressure, are ordinarily performed in a special hydrogenator, but this is not always necessary. Both the catalyst and the hydrogen may be generated *in situ,* from H_2PtCl_6,[109] and then ordinary glassware may be used.

---

[103] Stevens, Freeman, and Noll, *J. Org. Chem.* **31**, 3718 (1965).

[104] Brown, Heydkamp, Breuer, and Murphy, *J. Am. Chem. Soc.* **86**, 3565 (1964).

[105] Hoover and Rothrock, *J. Org. Chem.* **28**, 2082 (1963).



28

Although catalytic hydrogenation is the method which is most often used, double bonds may be reduced by other reagents as well. Among these are sodium in ethanol, chromous ion,[110] zinc and acids, lithium and aliphatic amines (see also reaction **5-12**),[111] hydrazine (if a small amount of oxidizing agent, such as air, H_2O_2, or cupric ion is present),[112] and NH_2OSO_3H.[113] However, metallic hydrides, such as lithium aluminum hydride and sodium borohydride, do not in general reduce carbon-carbon double or triple bonds,[114] although this can be done in special cases where the double or triple bond is polar, as in fulvenes (p. 42). In addition, lithium aluminum hydride often reduces double bonds which are in conjugation with C=O bonds, as well as reducing the C=O bonds, e.g.:[115]

---

[106] For reviews of catalytic hydrogenation, see Adkins and Shriner, in Gilman, "Advanced Organic Chemistry," 2d ed., vol. 1, pp. 779–834, John Wiley & Sons, Inc., New York, 1943; House, "Modern Synthetic Reactions," pp. 1–22, W. A. Benjamin, Inc., New York, 1965; and McQuillin, in Bentley, "Elucidation of Structures by Physical and Chemical Methods," Part 1, pp. 497–580, vol. XI of Weissberger, "Technique of Organic Chemistry," Interscience Publishers, Inc., New York, 1963.

[107] For a review of hydrogenations with Raney nickel, see Schröter, in "Newer Methods of Preparative Organic Chemistry," vol. 1, pp. 61–101, Interscience Publishers, Inc., New York, 1948.

[108] For a review of hydrogenations with copper chromite, see Grundmann, in "Newer Methods of Preparative Organic Chemistry," vol. 1, pp. 103–123, Interscience Publishers, Inc., New York, 1948.

[109] Brown and Sivasankaran, *J. Am. Chem. Soc.* **84,** 2828 (1962); Brown and Brown, *J. Am. Chem. Soc.* **84,** 1494, 1495, 2829 (1962); Brown, Sivasankaran, and Brown, *J. Org. Chem.* **28,** 214 (1963).

[110] For example, see Castro and Stephens, *J. Am. Chem. Soc.* **86,** 4358 (1964).

[111] Benkeser, Schroll, and Sauve, *J. Am. Chem. Soc.* **77,** 3378 (1955).

$$\mathrm{Ph{-}CH{=}CH{-}COOH} \xrightarrow{\mathrm{LiAlH_4}} 85\%\ \mathrm{Ph{-}CH_2{-}CH_2{-}CH_2OH}$$

This double reduction can be avoided by the use of aluminum hydride, which selectively reduces C=O groups in the presence of conjugated C=C bonds.[116] On the other hand, C=C bonds can be selectively reduced in the presence of conjugated COOR groups with $NaBH_4$.[117]

The inertness of ordinary double bonds toward metallic hydrides is quite useful, since it permits reduction of, say, a carbonyl or nitro group, without effect on a double bond in the same molecule (see Chapter 19 for a discussion of selectivity in reduction reactions).

Another hydrogenation method is called *transfer hydrogenation*.[118] In this method the hydrogen comes from another organic molecule, which is itself oxidized. A transition-metal catalyst is frequently employed. A common reducing agent is cyclohexene, which, when a palladium catalyst is used, is oxidized to benzene, losing two moles of hydrogen.

Triple bonds may be reduced, either by catalytic hydrogenation or by the other methods mentioned. The comparative reactivity of triple and double bonds depends on the catalyst.[119] With most catalysts (for example, Pd) triple bonds are hydrogenated more easily, and therefore it is possible to add just one mole of hydrogen and reduce a triple bond to a double bond, or to reduce a triple bond without affecting a double bond present in the same molecule. On the other hand, there are catalysts which selectively reduce double bonds.

An indirect method of double-bond reduction involves hydrolysis of boranes (prepared by reaction **5-13**). Trialkylboranes may be hydrolyzed by refluxing with carboxylic acids,[120] while monoalkylboranes RBH_2 may be hydrolyzed with base.[121] Triple bonds may be similarly reduced.[122] This method of reduction is useful for putting deuterium into a specific position of a molecule, since H-D exchange (see below) does not occur.

---

[112] Corey, Mock, and Pasto, *Tetrahedron Letters* **1961**, 347; Hünig, Müller, and Thier, *Tetrahedron Letters* **1961**, 353; Furst, Berlo, and Hooton, *Chem. Rev.* **65**, 51–68 (1965), pp. 64–65.

[113] Appel and Büchner, *Ann.* **654**, 1 (1962).

[114] For a review of the action of metallic hydrides on olefins and acetylenes, see Gaylord, "Reduction with Complex Metal Hydrides," pp. 925–975, Interscience Publishers, Inc., New York, 1956.

[115] Nystrom and Brown, *J. Am. Chem. Soc.* **69**, 2548 (1947).

[116] Jorgenson, *Tetrahedron Letters* **1962**, 559.

[117] Kadin, *J. Org. Chem.* **31**, 620 (1966).

[118] For a review, see Jackman, *Advan. Org. Chem.* **2**, 329–366 (1960).

[119] For a discussion of this, see Wells, *Chem. Ind.* (*London*) **1964**, 1742.

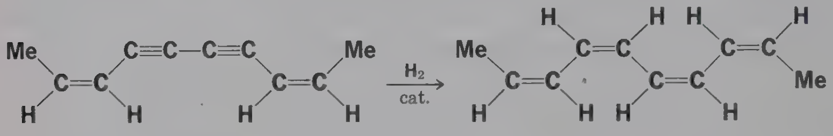
[120] Brown and Murray, *J. Am. Chem. Soc.* **81**, 4108 (1959).

[121] Weinheimer and Marisco, *J. Org. Chem.* **27**, 1926 (1962).

[122] Brown and Zweifel, *J. Am. Chem. Soc.* **81**, 1512 (1959).

Conjugated dienes may add hydrogen by 1,2 or 1,4 addition. Allenes can be singly hydrogenated to give olefins but more often take up two moles of hydrogen.

Most catalytic reductions of double or triple bonds have been shown to be cis, with the hydrogens entering from the less hindered side of the molecule.[123] Stereospecificity can be investigated only for tetrasubstituted olefins, which are the hardest to hydrogenate, but the results of these investigations show that the addition is usually 80 to 100% cis, though some of the trans addition product is normally also found and in some cases predominates. Catalytic hydrogenation of alkynes nearly always is stereoselective, giving the cis olefin (usually at least 80%), even when it is thermodynamically less stable. For example, **29** gave **30**, even though the steric hindrance is such that a planar molecule is impossible.[124] This is thus a useful method of preparing such cis olefins. However, when steric hindrance is too great, then the trans olefin may be formed. One factor which complicates the study of the stereochemistry of catalytic hydrogenation is that exchange of hydrogens takes place, as can be shown by hydrogenation with deuterium. Thus deuterogenation of ethylene produced all the possible deuterated ethylenes and HD.[125] With 2-butene, it was found that double-bond migration, cis-trans isomerization, and even exchange of hydrogen with groups not on the double bond could occur; for example, $C_4H_2D_8$ and C_4HD_9 were detected on treatment of *cis*-2-butene with deuterium and a catalyst.[126] Indeed, *alkanes* have been found to exchange with deuterium over a catalyst, and even without deuterium, that is,



29 **30**

$$CH_4 + CD_4 \longrightarrow CHD_3 + CH_2D_2$$

in the gas phase, with a catalyst. All this makes it difficult to investigate the stereochemistry of catalytic hydrogenation.

It was mentioned that catalytic hydrogenation of triple bonds usually gives the cis olefin. Most of the other methods of triple-bond reduction lead to the more thermodynamically stable trans olefin. However, this is not the case with the method involving hydrolysis of boranes, which also gives the cis product.[122]

The mechanism of catalytic reduction of double bonds is not thoroughly understood because it is a very difficult reaction to study.[127] In addition to the difficulties caused by hydrogen exchange, there is also the fact that this is ordinarily a heterogeneous reaction, and so the kinetic data, though easy to obtain (measurement of decreasing hydrogen pressure), are difficult to interpret. The reaction *has* been carried out with soluble, basic, catalysts (for example, *tert*-BuOK), but here the mechanism is certainly different, with H_2 assuming the role of an acid and H^- being the nucleophilic attacking species.[128] The currently accepted mechanism of the ordinary two-phase reaction was originally proposed in 1934.[129] According to this, the olefin is adsorbed onto the surface of the metal, though the nature of the actual bonding is unknown,[130] despite many attempts to elucidate it.[131] The metallic site is usually indicated by an asterisk. In the second step, H_2 contributes a proton and an electron so that, in effect, an alkyl radical

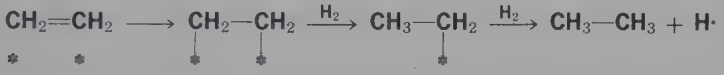
---

[123] For a review of the stereochemistry of catalytic hydrogenation, see Burwell, *Chem. Rev.* **57**, 895–934 (1957).

[124] Holme, Jones, and Whiting, *Chem. Ind.* (*London*) **1956**, 928.

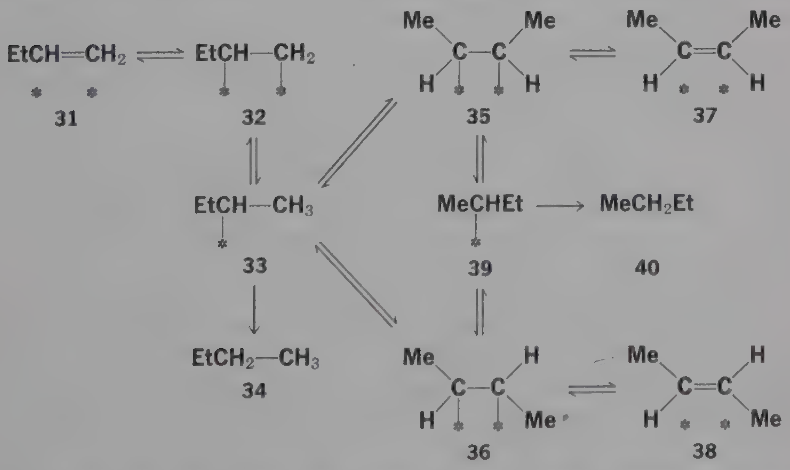
[125] Turkevich, Schissler, and Irsa, *J. Phys. Chem.* **55**, 1078 (1951).

[126] Wilson, Otvos, Stevenson, and Wagner, *Ind. Eng. Chem.* **45**, 1480 (1953).



$$\underset{*}{CH_2}{=}\underset{*}{CH_2} \longrightarrow \underset{*}{\overset{|}{CH_2}}{-}\underset{*}{\overset{|}{CH_2}} \xrightarrow{H_2} CH_3{-}\underset{*}{\overset{|}{CH_2}} \xrightarrow{H_2} CH_3{-}CH_3 + H\cdot$$

is created, still bound to the catalyst, but by only one bond. The other product of this step is another H·, which attacks a second complex, so that each H_2 molecule converts two bonded olefins to alkyl radicals. In the final step, the radical reacts with another H_2 molecule to give the reduction product, freed from the catalyst surface, and an H· radical. This is basically a free-radical process. All of the various side reactions, including hydrogen exchange and isomerism, may be explained by this type of scheme. For example, these steps may be occurring in hydrogenation of 1-butene:[132]



---

[127] For reviews, see Bond, *Quart. Rev. (London)* **8**, 279–307 (1954); Hoelscher, Poynter, and Weger, *Chem. Rev.* **54**, 575–592 (1954); and Burwell, *Chem. Eng. News* **44**, No. 34, 56–67 (Aug. 22, 1966).

[128] Walling and Bollyky, *J. Am. Chem. Soc.* **86**, 3750 (1964); Sloan, Matlack, and Breslow, *J. Am. Chem. Soc.* **85**, 4014 (1963).

[129] Horiuti and Polanyi, *Trans. Faraday Soc.* **30**, 1164 (1934).

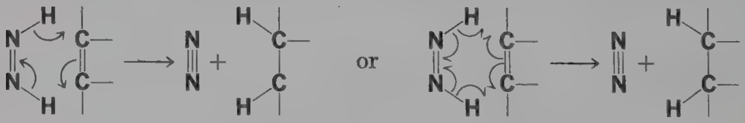
[130] See, for example, Burwell and Schrage, *J. Am. Chem. Soc.* **87**, 5234 (1965).

[131] See, for example, McKee, *J. Am. Chem. Soc.* **84**, 1109 (1962).

[132] Smith and Burwell, *J. Am. Chem. Soc.* **84**, 925 (1962).

In this scheme the normal reaction is represented by **31** → **32** → **33** → **34**; double-bond migration by **31** → **32** → **33** → **35** → **37**; cis-trans isomerization by **38** → **36** → **33** → **35** → **37**; and hydrogen exchange by **31** → **32** → **33** → **35** → **39** → **40**. Although the mechanism is satisfactory as far as it goes, there are questions it does not answer, besides the important ones about the nature of the asterisk and the nature of the bonding. One of these is, just where does the H_2 come from, and in what form does it come? It is possible, of course, that the H_2 comes from the vapor phase, in which case it approaches the molecule from the side opposite the one which was adsorbed onto the catalyst surface, and in which case it reacts as a hydrogen molecule. On the other hand many of the catalysts, including Raney nickel, have hydrogen adsorbed in them, and it may be that the hydrogen comes from the catalyst, in which case it comes from the same side as was adsorbed onto the catalyst, and in which case it *may* come in as hydrogen atoms.[133] It has been shown that platinum catalyzes homolytic cleavage of hydrogen molecules.[134] Another question is, what differences are caused by the different type of bonding to each catalyst? It is certain that the bond energy, and perhaps even the type of bonding, will be different for catalysts of different structure, but what effect this has on the mechanism is not known.[135]

In the reactions with hydrazine and with NH_2OSO_3H the actual reducing species is diimide, NH=NH, which is formed from the hydrazine by the oxidizing agent, and from NH_2OSO_3H by the intermediacy of $|\overline{N}H$, which dimerizes.[136] Although both the syn and anti forms of diimide are produced, only the syn form reduces the double bond,[137] by a cyclic mechanism:[138]



The latter process is more likely, since diimide reductions are most successful with symmetrical multiple bonds (C=C, C≡C, N=N, O=O) and are more difficult for those inherently polar (C≡N, C=N, C=O, etc.). Diimide is not stable enough for isolation, though both the syn and anti forms have been trapped in a solid nitrogen matrix, at 20°K.[139]

When double bonds are reduced by lithium in ammonia or amines, the mechanism is similar to that of the Birch reduction (reaction **5-12**).

Reductions of double and triple bonds are found at OS **I**, 101, 311; **II**, 191, 491; **III**, 385, 586, 742, 794; **IV**, 136, 298, 302, 304, 408, 887; **42**, 8.

Catalysts and apparatus for hydrogenation are found at OS **I**, 61, 463; **II**, 142; **III**, 176, 181, 685; **46**, 89.

---

[133] Kokes and Emmett, *J. Am. Chem. Soc.* **81**, 5032 (1959).

[134] Krasna, *J. Am. Chem. Soc.* **83**, 289 (1961).

[135] See Trapnell, *Quart. Rev. (London)* **8**, 404–421 (1961).

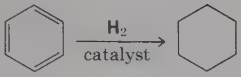
[136] For a review of hydrogenations with diimide, see Miller, *J. Chem. Educ.* **42**, 254–259 (1965). For a review of the formation and structure of diimides, see Hünig, Müller, and Thier, *Angew. Chem. Intern. Ed. Engl.* **4**, 271–280 (1965).

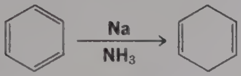
[137] Aylward and Sawistowska, *J. Chem. Soc.* **1964**, 1435.

[138] Ref. 112; van Tamelen, Dewey, Lease, and Pirkle, *J. Am. Chem. Soc.* **83**, 4302 (1961).

[139] Rosengren and Pimentel, *J. Chem. Phys.* **43**, 507 (1965).

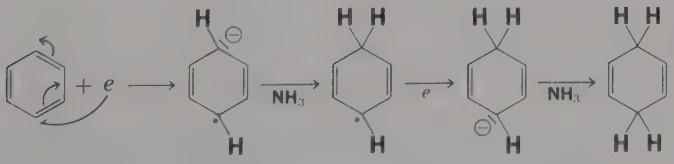
5-12 Hydrogenation of aromatic rings





Aromatic rings may be reduced by catalytic hydrogenation, but higher temperatures (100 to 200°) are required than for ordinary double bonds. Many functional groups, such as OH, O^-, COOH, COOR, NH_2, etc., do not interfere with the reaction, but some groups may be preferentially reduced. Among these are CH_2OH groups, which undergo hydrogenolysis to CH_3 (reaction **0-74**, p. 349). Phenols may be reduced to *cyclohexanones,* presumably through the enol. Heterocyclic compounds are often reduced. Thus furan gives tetrahydrofuran. With benzene rings it is usually impossible to stop the reaction after only one or two bonds have been reduced, since olefins are more easily reduced than aromatic rings. Thus, 1 mole of benzene, treated with 1 mole of hydrogen, gives no cyclohexadiene or cyclohexene, but $\frac{1}{3}$ mole of cyclohexane and $\frac{2}{3}$ mole of recovered benzene. This is not true for all aromatic systems. With phenanthrene, for example, it is easy to stop after only the 9,10-bond has been reduced (see p. 39).

When aromatic rings are reduced by sodium (or potassium or lithium) in liquid ammonia, 1,4 addition of hydrogen takes place, and nonconjugated cyclohexadienes are produced. This reaction is called the *Birch reduction.*[140] On substituted aromatic compounds Birch reduction takes place so that the minimum possible number of alkyl or alkoxyl groups are on the reduced positions. Thus anisole gives 1-methoxy-1,4-cyclohexadiene and not 1-methoxy-2,5-cyclohexadiene. The mechanism involves direct transfer of electrons from the metal:[141]



41 **42**

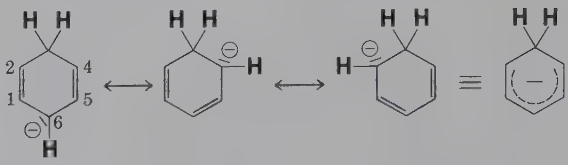
The sodium transfers an electron to the ring, becoming oxidized to Na^+ and creating an ion-radical (**41**). There is a great deal of evidence from electron-spin resonance for these species. The ion-radical accepts a proton from the solvent to give a radical, which is reduced to a carbanion by another sodium atom. Finally, **42** accepts another proton. Electron-withdrawing groups on a ring accelerate the reaction, and electron-donating groups retard it. Ordinary olefins are usually unaffected by these conditions, and double bonds may be present in the molecule, if they are not conjugated with the ring. However, phenylated olefins, alkynes, and conjugated olefins (with C═C or C═O) are reduced under these conditions.

---

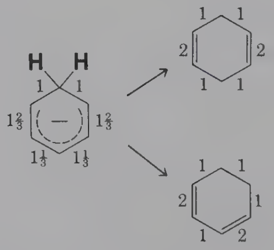
[140] For reviews, see Birch, *Quart. Rev. (London)* **4,** 69–93 (1950); Birch and Smith, *Quart. Rev. (London)* **12,** 17–33 (1958); House, "Modern Synthetic Reactions," pp. 50–54, 61–72, W. A. Benjamin, Inc., New York, 1965.

[141] Birch and Nasipuri, *Tetrahedron* **6,** 148 (1959).

It may be noted that **42** is a resonance hybrid; that is, we may write two additional canonical forms:



The question therefore arises, why does the carbanion pick up a proton at the 6-position to give the 1,4-diene? Why not at the 2- or 4-position to give the 1,3-diene? An answer to this question has been proposed by Hine, who has suggested that this case is an illustration of the operation of the *principle of least motion.*[142] According to this principle, "those elementary reactions will be favored that involve the least change in atomic position and electronic configuration."[142] The principle may be applied to the case at hand in the following manner (simplified): The valence-bond bond orders (p. 28) for the six carbon-carbon bonds (on the assumption that each of the three forms contributes equally) are (going around the ring) $1\frac{2}{3}$, 1, 1, $1\frac{2}{3}$, $1\frac{1}{3}$, and $1\frac{1}{3}$. When the carbanion is converted to the diene, these bond orders change as follows:



It may be seen that the two bonds whose bond order = 1 are unchanged in the two products, but for the other four bonds there is a change. If the 1,4-diene is formed, the change is $\frac{1}{3} + \frac{1}{3} + \frac{1}{3} + \frac{1}{3}$, while formation of the 1,3-diene requires a change of $\frac{1}{3} + \frac{2}{3} + \frac{2}{3} + \frac{1}{3}$. Since a greater change is required in order to form the 1,3-diene, the principle of least motion predicts formation of the 1,4-diene.

Reduction of aromatic rings with lithium in amines (instead of ammonia) proceeds further, and cyclohexenes are obtained.[143] It is thus possible to reduce a benzene ring, by proper choice of reagent, so that one, two, or all three double bonds are reduced. It has been shown that it is possible to reduce either one or two double bonds by electrochemical reduction.[144]

---

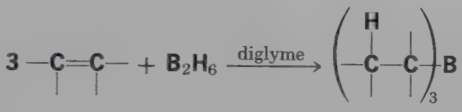
[142] Hine, *J. Org. Chem.* **31,** 1236 (1966).

[143] Benkeser, Robinson, Sauve, and Thomas, *J. Am. Chem. Soc.* **77,** 3230 (1955); Benkeser, Agnihotri, and Burrous, *Tetrahedron Letters* **1960,** No. 16, 1; Benkeser, Burrous, Hazdra, and Kaiser, *J. Org. Chem.* **28,** 1094 (1963); Benkeser, Agnihotri, Burrous, Kaiser, Mallan, and Ryan, *J. Org. Chem.* **29,** 1313 (1964).

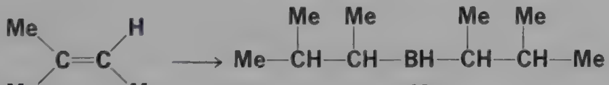
OS **I,** 99, 499; **II,** 566; **III,** 278, 742; **IV,** 313, 887, 903; **41,** 56; **42,** 48, 62; **43,** 22; **44,** 86.

F. Boron on the other side

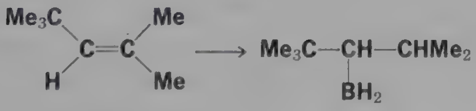
5-13 Hydroboration



Borane, BH_3, is not a known compound, but when olefins are treated with diborane in diglyme (the dimethyl ether of diethylene glycol), BH_3 adds across the double bond. Ordinarily the process cannot be stopped at this point, for the resulting RBH_2 adds to another molecule of olefin to give R_2BH, which in turn adds to a third olefin molecule, so that the isolated product is a trialkylborane, R_3B.[145] The reaction can be performed on alkenes with one to four substituents, including cyclic olefins, but when the olefin is highly hindered, the product *is* the dialkylborane R_2BH, or even the monoalkylborane RBH_2. For example, **43** and **45** have been prepared in this manner:



43



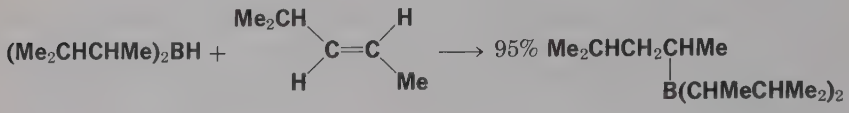
44 **45**

In all cases the boron goes to the side of the double bond which has more hydrogens, whether the substituents are aryl or alkyl. Thus hydroboration of **44** gives 98% **45** and only 2% of the other product. This actually follows Markovnikov's rule, since boron is more positive than hydrogen. When both sides of the double bond are monosubstituted, or both disubstituted, then about equal amounts of each isomer are obtained. However, it is possible in such cases to make the addition selective by the use of a large attacking molecule. For example, treatment of *iso*-PrCH=CHMe with diborane gave 57% of product with the boron on the methyl-bearing carbon and 43% of the other, while treatment with **43** (called *disiamylborane*) gave 95% of **46** and only 5% of the other isomer:[146]

---

[144] Benkeser and Kaiser, *J. Am. Chem. Soc.* **85,** 2858 (1963).

[145] For a monograph on this reaction, and its manifold applications, see Brown, "Hydroboration," W. A. Benjamin, Inc., New York, 1962. For reviews, see Zweifel and Brown, *Org. Reactions* **13,** 1–54 (1963); Brown, *Tetrahedron* **12,** 117–138 (1961).

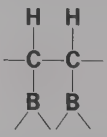


43 **46**

Diborane is quite unselective and attacks all sorts of double bonds. Disiamylborane and similar molecules are far more selective and will preferentially attack less hindered bonds, so that it is often possible to hydroborate one double bond in a molecule selectively and leave others unaffected.[147]

The principal use of the hydroboration reaction is that alkylboranes, when oxidized with hydrogen peroxide and NaOH, are converted to alcohols (reaction **9-33,** p. 889). This thus becomes an indirect way of adding H_2O across a double bond in an anti-Markovnikov manner. However, boranes undergo other reactions as well: they can be reduced with carboxylic acids, providing an indirect method for reduction of double bonds (reaction **5-11**); or they can be oxidized with chromic acid to give ketones,[148] dimerized with silver nitrate and NaOH (reaction **4-23,** p. 556), or isomerized (reaction **8-12,** p. 814). They are thus useful intermediates for the preparation of a wide variety of compounds. In addition to alkyl and aryl groups, such functional groups as alkoxy, halogen, and COOR may be present in the molecule, but not groups which are reducible by diborane.

The double bonds in a diene are apparently hydroborated separately; that is, there is no 1,4 addition. However, it is not easy to hydroborate just one of a conjugated system, since conjugated double bonds are less reactive than isolated ones. Triple bonds may be hydroborated to unsaturated boranes, which can be oxidized and hydrolyzed to aldehydes and ketones. It is also possible for triple bonds to be bis-hydroborated to compounds of the type[149]



The addition in hydroboration has been shown to be stereoselective and cis, with attack taking place from the less hindered side.[150] Where the reaction rates are measurable (most are too fast), the reaction is second order.[151]

---

[146] Brown and Zweifel, *J. Am. Chem. Soc.* **83,** 1241 (1961).

[147] Brown and Moerikofer, *J. Am. Chem. Soc.* **85,** 2063 (1963); Zweifel and Brown, *J. Am. Chem. Soc.* **85,** 2066 (1963); Zweifel, Ayyangar, and Brown, *J. Am. Chem. Soc.* **85,** 2072 (1963).

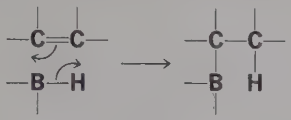
[148] Brown and Garg, *J. Am. Chem. Soc.* **83,** 2951 (1961). See also Lansbury and Nienhouse, *Chem. Commun.* **1966,** 273.

[149] Pasto, *J. Am. Chem. Soc.* **86,** 3039 (1964).

[150] Brown and Zweifel, *J. Am. Chem. Soc.* **83,** 2544 (1961).

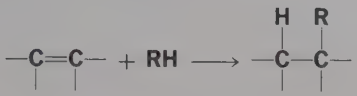
[151] Brown and Moerikofer, *J. Am. Chem. Soc.* **83,** 3417 (1961).

The mechanism is probably a cyclic four-center one:



G. Carbon on the other side

5-14 Addition of alkanes and alkenes

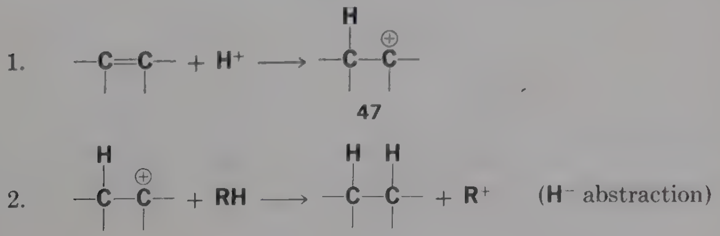


$$-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}- + RH \longrightarrow -\overset{H}{\overset{|}{\underset{|}{C}}}-\overset{R}{\overset{|}{\underset{|}{C}}}-$$

There are two important ways of adding alkanes to olefins: the thermal method and the acid-catalysis method.[152] Both give chiefly mixtures, and neither is useful for the preparation of relatively pure compounds in reasonable yields. However, both are useful industrially. In the thermal method the reactants are heated to high temperatures (about 500°) at high pressures (150 to 300 atm) without a catalyst. As an example, propane and ethylene gave 55.5% isopentane, 7.3% hexanes, 10.1% heptanes, and 7.4% alkenes.[153] The mechanism is undoubtedly of a free-radical type and may be illustrated by one possible sequence in the reaction between propane and ethylene:

1. $CH_3CH_2CH_3 \xrightarrow[\Delta]{} CH_3\cdot + CH_3CH_2\cdot$
2. $CH_3\cdot + CH_3CH_2CH_3 \longrightarrow CH_4 + CH_3\underset{\cdot}{C}HCH_3$
3. $CH_3\underset{\cdot}{C}HCH_3 + CH_2{=}CH_2 \longrightarrow (CH_3)_2CHCH_2CH_2\cdot$
4. $(CH_3)_2CHCH_2CH_2\cdot + CH_3CH_2CH_3 \longrightarrow (CH_3)_2CHCH_2CH_3 + CH_3\underset{\cdot}{C}HCH_3$

In the acid-catalysis method, a proton or Lewis acid is used as the catalyst, and the reaction is carried out at temperatures between –30 and 100°. This is a Friedel-Crafts process with a carbonium-ion mechanism (illustrated for a proton acid catalyst):



1. $-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}- + H^+ \longrightarrow -\overset{H}{\overset{|}{\underset{|}{C}}}-\overset{\oplus}{\underset{|}{C}}-$

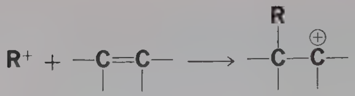
47

2. $-\overset{H}{\overset{|}{\underset{|}{C}}}-\overset{\oplus}{\underset{|}{C}}- + RH \longrightarrow -\overset{H}{\overset{|}{\underset{|}{C}}}-\overset{H}{\overset{|}{\underset{|}{C}}}- + R^+$ (H^- abstraction)

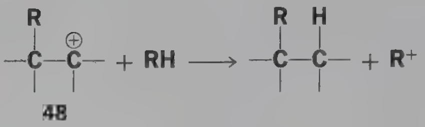
---

[152] For a review, see Schmerling, in Olah, "Friedel-Crafts and Related Reactions," vol. 2, pp. 1075–1111, 1121–1122, Interscience Publishers, Inc., New York, 1964.

[153] Frey and Hepp, *Ind. Eng. Chem.* **28**, 1439 (1936).

3. 

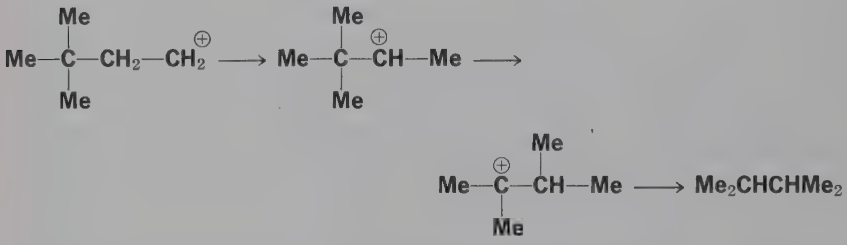
$$R^+ + -\underset{|}{C}{=}\underset{|}{C}- \longrightarrow -\overset{\overset{R}{|}}{\underset{|}{C}}-\overset{\oplus}{\underset{|}{C}}-$$

4.  (H⁻ abstraction)

$$-\overset{\overset{R}{|}}{\underset{|}{C}}-\overset{\oplus}{\underset{|}{C}}- + RH \longrightarrow -\overset{\overset{R}{|}}{\underset{|}{C}}-\overset{\overset{H}{|}}{\underset{|}{C}}- + R^+$$

48

However, since **48** (by Markovnikov's rule) is usually a primary carbonium ion, it often rearranges before it abstracts a hydride ion, explaining, for example, why the principal product from the reaction between isobutane and ethylene is 2,3-dimethylbutane:



$$Me-\overset{\overset{Me}{|}}{\underset{\underset{Me}{|}}{C}}-CH_2-\overset{\oplus}{CH_2} \longrightarrow Me-\overset{\overset{Me}{|}}{\underset{\underset{Me}{|}}{C}}-\overset{\oplus}{CH}-Me \longrightarrow Me-\overset{\oplus}{\underset{\underset{Me}{|}}{C}}-\overset{\overset{Me}{|}}{CH}-Me \longrightarrow Me_2CHCHMe_2$$

It is also possible for **47** (or **48**, for that matter), instead of abstracting a hydride ion, to add to another mole of olefin, so that not only rearrangement products but also dimeric and polymeric products are frequent.

The reaction may also be base-catalyzed, in which case there is nucleophilic addition and a carbanion mechanism. For example, toluene adds to styrene in the presence of sodium to give 1,3-diphenylpropane:[154]

$$PhCH_3 \xrightarrow{Na} Ph\bar{C}H_2^{\ominus} + PhCH{=}CH_2 \longrightarrow Ph\overset{\ominus}{\bar{C}}H-CH_2CH_2Ph \xrightarrow{\text{solvent}} PhCH_2CH_2CH_2Ph$$

This reaction has been performed with salts of carboxylic acids in what amounts to a method of alkylation of carboxylic acids:[155]

$$CH_3COOK \xrightarrow{NaNH_2} {}^{\ominus}\bar{C}H_2COOK + CH_2{=}CH_2 \longrightarrow {}^{\ominus}\bar{C}H_2-CH_2CH_2COOK$$

Two and even three alkyl groups may be put on this way.

As pointed out above, it is possible in the acid-catalyzed process for an olefin to add to an olefin so that the product is a dimer which contains one double bond, e.g.,

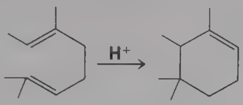
$$CH_2{=}CH_2 + CH_2{=}CH_2 \longrightarrow CH_2{=}CH-CH_2-CH_3$$

---

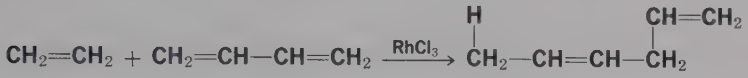
[154] Pines and Wunderlich, *J. Am. Chem. Soc.* **80**, 6001 (1958).

[155] Schmerling and Toekelt, *J. Am. Chem. Soc.* **84**, 3694 (1962).

This reaction has also been carried out internally, e.g.,

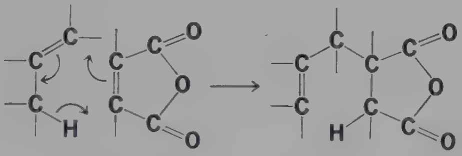


Rhodium chloride catalyzes the 1,4 addition of olefins to dienes, e.g.,[156]

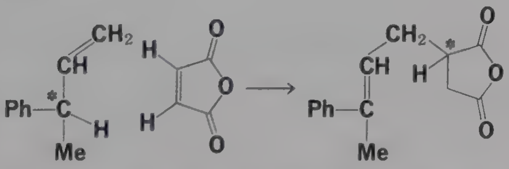


$$CH_2{=}CH_2 + CH_2{=}CH{-}CH{=}CH_2 \xrightarrow{RhCl_3} \overset{H}{\overset{|}{C}}H_2{-}CH{=}CH{-}\overset{CH=CH_2}{\overset{|}{C}}H_2$$

as well as the simple addition of olefins to olefins. Olefins can add to double bonds in another way, which is, however, still formally the addition of RH to a double bond, e.g.,



This type of reaction is called the *ene synthesis*[157] and bears a certain similarity to the Diels-Alder reaction (reaction **5-34**). It is carried out with dienophiles, such as maleic anhydride. That the mechanism is a cyclic, six-center one, as shown above, was demonstrated by the reaction between optically active $PhCHMeCH{=}CH_2$ and maleic anhydride, in which the product was optically active.[158]

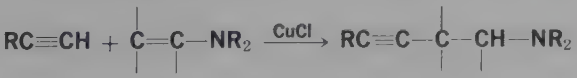


Only a six-center mechanism is consistent with this result. Incidentally, this represents another case of "asymmetric synthesis" (p. 90).

In the presence of cuprous chloride and ammonium chloride, acetylene adds to another molecule of itself to give vinylacetylene:

$$HC{\equiv}CH + HC{\equiv}CH \xrightarrow[NH_4Cl]{CuCl} HC{\equiv}C{-}CH{=}CH_2$$

Similarly, terminal alkynes add to the double bond of enamines:[159]



$$RC{\equiv}CH + \underset{|}{\overset{|}{C}}{=}\underset{|}{C}{-}NR_2 \xrightarrow{CuCl} RC{\equiv}C{-}\underset{|}{\overset{|}{C}}{-}\underset{|}{C}H{-}NR_2$$

---

[156] Alderson, Jenner, and Lindsey, *J. Am. Chem. Soc.* **87**, 5638 (1965).

[157] Alder and Brachel, *Ann.* **651**, 141 (1962).

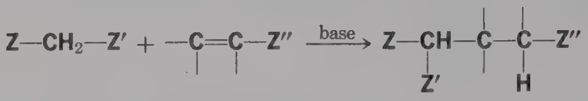
[158] Hill and Rabinovitz, *J. Am. Chem. Soc.* **86**, 965 (1964).

[159] Brannock, Burpitt, and Thweatt, *J. Org. Chem.* **28**, 1462 (1963).

Olefins and alkynes may also add to each other to give cyclic products (see reactions **5-35** and **5-36**).

OS **I**, 229; **IV**, 665, 766; **43**, 27.

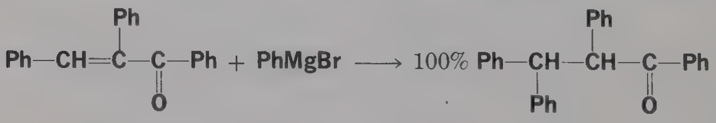
5-15 The Michael reaction



$$\text{Z—CH}_2\text{—Z}' + \text{—}\underset{|}{\text{C}}=\underset{|}{\text{C}}\text{—Z}'' \xrightarrow{\text{base}} \text{Z—}\underset{\text{Z}'}{\underset{|}{\text{CH}}}\text{—}\overset{|}{\underset{|}{\text{C}}}\text{—}\overset{|}{\underset{\text{H}}{\underset{|}{\text{C}}}}\text{—Z}''$$

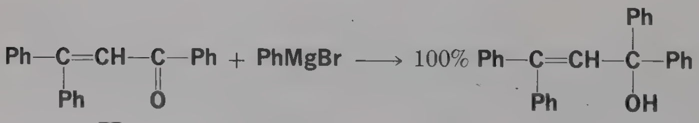
Compounds containing electron-withdrawing groups (Z is defined on p. 568) add, in the presence of bases, to olefins of the form C═C—Z (including quinones). This is called the *Michael reaction.* The base removes the acidic proton, and then the mechanism is as outlined on page 568. The reaction has been carried out with malonates, cyanoacetates, acetoacetates, other β-keto esters, and compounds of the form Z—CH_3, ZCH_2R, ZCHR_2, and ZCHRZ′, including esters, ketones, aldehydes, nitriles, nitro compounds, and sulfones, as well as other compounds with relatively acidic hydrogens, such as indenes and fluorenes.[160] These reagents do not add to ordinary double bonds, except in the presence of free-radical initiators (reaction **5-16**). 1,2 addition (to the C═O or C≡N group) often competes and sometimes predominates (reaction **6-41,** p. 697).

A closely related reaction is the addition of Grignard reagents to compounds of the form C═C—C═O (or C═C—C≡N). In this reaction 1,2 addition is more important than it is with the nucleophiles considered earlier. The product is often controlled by steric factors. Thus, **49** with phenylmagnesium bromide gives 100% 1,4 addition, while **50** gives 100% 1,2 addition:



$$\text{Ph—CH}=\overset{\text{Ph}}{\overset{|}{\text{C}}}\text{—}\underset{\text{O}}{\underset{\|}{\text{C}}}\text{—Ph} + \text{PhMgBr} \longrightarrow 100\%\ \text{Ph—}\underset{\text{Ph}}{\underset{|}{\text{CH}}}\text{—}\overset{\text{Ph}}{\overset{|}{\text{CH}}}\text{—}\underset{\text{O}}{\underset{\|}{\text{C}}}\text{—Ph}$$

49



$$\text{Ph—}\underset{\text{Ph}}{\underset{|}{\text{C}}}=\text{CH—}\underset{\text{O}}{\underset{\|}{\text{C}}}\text{—Ph} + \text{PhMgBr} \longrightarrow 100\%\ \text{Ph—}\underset{\text{Ph}}{\underset{|}{\text{C}}}=\text{CH—}\overset{\text{Ph}}{\overset{|}{\underset{\text{OH}}{\underset{|}{\text{C}}}}}\text{—Ph}$$

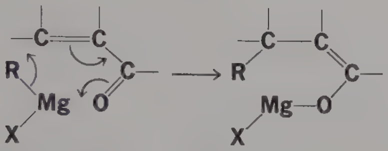
50

In general, substitution at the carbonyl group increases 1,4 addition, while substitution at the double bond increases 1,2 addition. In most cases both products are obtained, but α,β-unsaturated *aldehydes* nearly always give exclusive 1,2 addition. The extent of 1,4 addition of Grignard reagents is increased by the use of a cuprous chloride catalyst. Alkyllithiums, treated with compounds of the form C=C—$COCH_3$ and C=C—$COOC_2H_5$, gave only 1,2 addition.[161] In some cases, with Grignard reagents, it is possible to get a diaddition product (1,2 *and* 1,4).[162] Grignard reagents also add to polyhalo olefins. However, Grignard reagents generally do not add to ordinary C=C double bonds (see, however, reaction **5-39**).

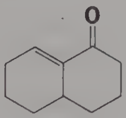
---

[160] For reviews, see Bergmann, Ginsburg, and Pappo, *Org. Reactions* **10,** 179–560 (1959); Bruson, *Org. Reactions* **5,** 79–135 (1949) (for acrylonitrile); and House, "Modern Synthetic Reactions," pp. 204–215, W. A. Benjamin, Inc., New York, 1965.

It has been postulated that the 1,4 addition of Grignard reagents proceeds by a six-centered cyclic mechanism:

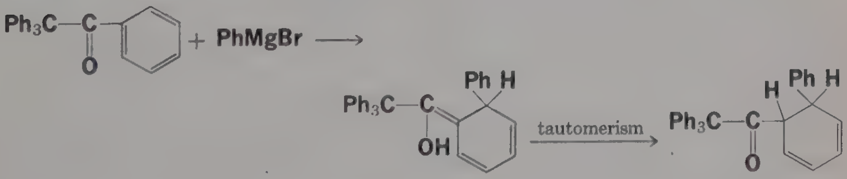


This would be in accord with the decrease in the amount of 1,4 addition with increased substitution at the 4-position.[163] On the other hand, the following is evidence against this mechanism: the mechanism obviously requires the two double bonds to be in the cisoid conformation. It has been shown[164] that **51**, which must be in this conformation, gave only 43% 1,4 addition, while $CH_3CH=CHCOCH_3$, which can adopt any conformation, gave 50% 1,4 addition.



51

In certain cases, Grignard reagents add 1,4 to *aromatic* systems, for example,[165]



Such cyclohexadienes are easily oxidizable to benzenes (often by atmospheric oxygen), so that this reaction becomes a method of alkylating and arylating suitably substituted (usually hindered) aryl ketones. A similar reaction has been reported for aromatic nitro compounds:[166]

---

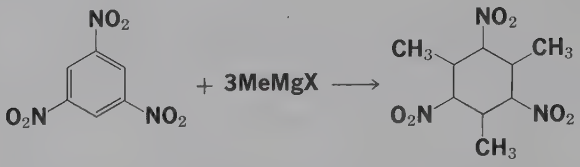
[161] Rozhkov and Makin, *J. Gen. Chem. USSR* **34**, 57 (1964).

[162] Fuson, San, and Dieckmann, *J. Org. Chem.* **27**, 1221 (1962).

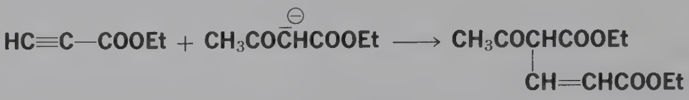
[163] For a discussion of this, see Wright, in Newman, "Steric Effects in Organic Chemistry," pp. 406–416, John Wiley & Sons, Inc., New York, 1956.

[164] House and Thompson, *J. Org. Chem.* **28**, 360 (1963). For further evidence against the cyclic mechanism, see Klein, *Tetrahedron* **20**, 465 (1964).

[165] This example is from Schmidlin and Wohl, *Ber.* **43**, 1145 (1910), and Mosher and Huber, *J. Am. Chem. Soc.* **75**, 4604 (1953). For a review of such reactions, see Fuson, *Advan. Organometal. Chem.* **1**, 221–238 (1964).



Michael reactions and 1,4 Grignard additions are sometimes applied to substrates of the type C≡C—Z, e.g.,

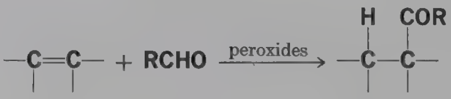


$$\mathrm{HC{\equiv}C{-}COOEt} + \mathrm{CH_3CO\overset{\ominus}{C}HCOOEt} \longrightarrow \mathrm{CH_3CO\underset{CH{=}CHCOOEt}{\underset{|}{C}H}COOEt}$$

Acetylene reacts with nitromethane to give $CH_3CH{=}CHNO_2$, which arises from rearrangement of the initially formed $CH_2{=}CHCH_2NO_2$.

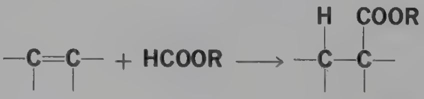
OS **I,** 272; **II,** 200; **III,** 286; **IV,** 93, 630, 652, 662, 776; **41,** 38, 60.

5-16 Addition of alcohols, amines, esters, aldehydes, etc.

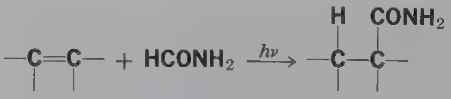


$$\mathrm{-\underset{|}{C}{=}\underset{|}{C}-} + \mathrm{RCHO} \xrightarrow{\text{peroxides}} \mathrm{-\overset{H}{\underset{|}{C}}-\overset{COR}{\underset{|}{C}}-}$$

Aldehydes, formates, primary and secondary alcohols, amines, alkyl halides,[167] compounds of the type Z—CH_2—Z′, and a few other compounds add to double bonds in the presence of free-radical initiators.[168] This is formally the addition of RH to a double bond, but the "R" is not just any carbon, but one connected to an oxygen or a nitrogen, a halogen, or to two Z groups (defined as on p. 357). The addition of aldehydes is illustrated above. Formates and formamides[169] add similarly:



$$\mathrm{-\underset{|}{C}{=}\underset{|}{C}-} + \mathrm{HCOOR} \longrightarrow \mathrm{-\overset{H}{\underset{|}{C}}-\overset{COOR}{\underset{|}{C}}-}$$



$$\mathrm{-\underset{|}{C}{=}\underset{|}{C}-} + \mathrm{HCONH_2} \xrightarrow{h\nu} \mathrm{-\overset{H}{\underset{|}{C}}-\overset{CONH_2}{\underset{|}{C}}-}$$

---

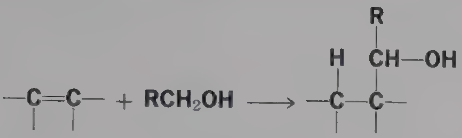
[166] Severin and Schmitz, *Chem. Ber.* **96,** 3081 (1963).

[167] Trecker and Henry, *Chem. Commun.* **1966,** 258.

[168] For reviews, see Walling and Huyser, *Org. Reactions* **13,** 91–149 (1963), pp. 108–112, 132–146; Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," pp. 121–152, The Macmillan Company, New York, 1964; Walling, "Free Radicals in Solution," pp. 273–289, John Wiley & Sons, Inc., New York, 1957.

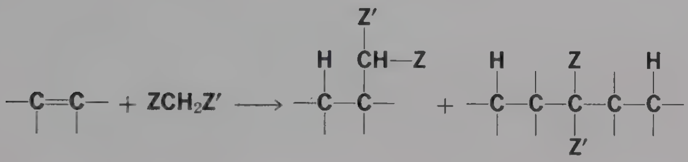
[169] Elad and Rokach, *J. Org. Chem.* **29,** 1855 (1964), **30,** 3361 (1965), *J. Chem. Soc.* **1965,** 800.

Alcohols, amines, and alkyl halides add as follows (shown for alcohols):



$$-\underset{|}{C}=\underset{|}{C}- + RCH_2OH \longrightarrow -\overset{H}{\underset{|}{C}}-\overset{\overset{R}{|}}{\overset{CH-OH}{\underset{|}{C}}}-$$

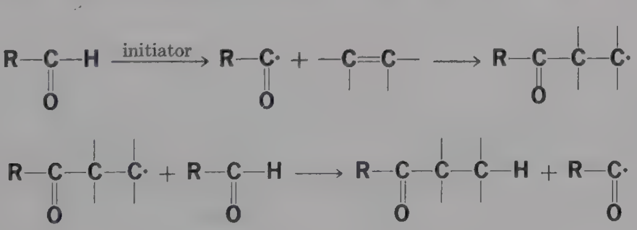
ZCH_2Z' compounds react at the carbon bearing the active hydrogen:[170]



$$-\underset{|}{C}=\underset{|}{C}- + ZCH_2Z' \longrightarrow -\overset{H}{\underset{|}{C}}-\overset{\overset{Z'}{|}}{\overset{CH-Z}{\underset{|}{C}}}- + -\overset{H}{\underset{|}{C}}-\underset{|}{\overset{|}{C}}-\underset{Z'}{\overset{Z}{C}}-\underset{|}{\overset{|}{C}}-\overset{H}{\underset{|}{C}}-$$

Similar additions have been successfully carried out with carboxylic acids, acyl halides, esters, nitriles, and other types of compounds.[171]

These reactions are most successful when the olefin contains electron-withdrawing groups such as halo or carbonyl groups. A free-radical initiator is required, usually peroxides or ultraviolet light. The mechanism may be illustrated for aldehydes but is similar for the other compounds:



$$R-\underset{O}{\underset{\|}{C}}-H \xrightarrow{\text{initiator}} R-\underset{O}{\underset{\|}{C}}\cdot + -\underset{|}{C}=\underset{|}{C}- \longrightarrow R-\underset{O}{\underset{\|}{C}}-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}\cdot$$

$$R-\underset{O}{\underset{\|}{C}}-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}\cdot + R-\underset{O}{\underset{\|}{C}}-H \longrightarrow R-\underset{O}{\underset{\|}{C}}-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-H + R-\underset{O}{\underset{\|}{C}}\cdot$$

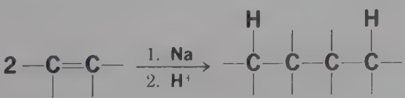
etc.

Polymers are often side products.

Similar reactions have been carried out on acetylene.[172]

OS **IV**, 430.

5-17 Reductive coupling of olefins



$$2-\underset{|}{C}=\underset{|}{C}- \xrightarrow[\text{2. }H^+]{\text{1. Na}} -\overset{H}{\underset{|}{C}}-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-\overset{H}{\underset{|}{C}}-$$

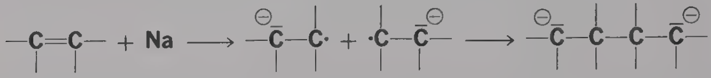
---

[170] For example, see Allen, Cadogan, Harris, and Hey, *J. Chem. Soc.* **1962**, 4468.

[171] Allen, Cadogan, and Hey, *J. Chem. Soc.* **1965**, 1918.

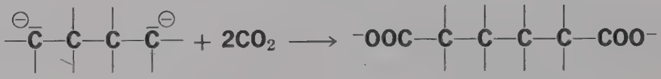
[172] For example, see Cywinski and Hepp, *J. Org. Chem.* **31**, 3814 (1965); and DiPietro and Roberts, *Angew. Chem. Intern. Ed. Engl.* **5**, 415 (1966).

Certain olefins have been coupled by treatment with sodium, followed by acid. The reaction has been performed with styrene, 1,1-diphenylethylene, and butadiene, among others.[173] The coupling is head to head. The first step is probably an electron transfer from the sodium, creating an ion-radical, which dimerizes:



$$-\underset{|}{C}=\underset{|}{C}- + \text{Na} \longrightarrow -\overset{\ominus}{\underset{|}{\bar{C}}}-\overset{|}{\underset{|}{C}}\cdot + \cdot\overset{|}{\underset{|}{C}}-\overset{\ominus}{\underset{|}{\bar{C}}}- \longrightarrow -\overset{\ominus}{\underset{|}{\bar{C}}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{\ominus}{\underset{|}{\bar{C}}}-$$

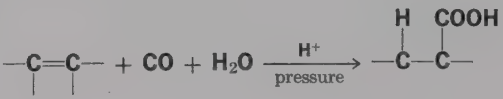
That the dicarbanion is an intermediate may be shown by treatment of the mixture with carbon dioxide, instead of acid, whereupon a dicarboxylate ion is obtained:



$$-\overset{\ominus}{\underset{|}{\bar{C}}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{\ominus}{\underset{|}{\bar{C}}}- + 2CO_2 \longrightarrow {}^{-}OOC-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-COO^{-}$$

Similar reactions have been carried out electrolytically.[174]

5-18 Hydrocarboxylation



$$-\underset{|}{C}=\underset{|}{C}- + CO + H_2O \xrightarrow[\text{pressure}]{H^+} -\overset{\overset{\displaystyle H}{|}}{C}-\overset{\overset{\displaystyle COOH}{|}}{C}-$$

Olefins may be hydrocarboxylated in a number of ways.[175] In one method, the olefin is treated with carbon monoxide and water at 100 to 350° and 500 to 1000 atm pressure, with a mineral-acid catalyst. However, the reaction may also be performed under milder conditions. If the olefin is first treated with CO and catalyst, and then water added, the reaction may be accomplished at 0 to 50° and 1 to 100 atm. If formic acid is used as the source of both the CO and the water, the reaction may be carried out at room temperature and atmospheric pressure.

Hydrocarboxylation may also be accomplished under mild conditions (160° and 50 atm) by the use of nickel carbonyl as catalyst. This is more often applied to triple bonds, to give α,β-unsaturated acids, in which cases the conditions are milder still. Acid catalysts are used along with the nickel carbonyl, but basic catalysts may also be employed.[176]

In another method, the palladium chloride complex of the olefin is treated with CO in ethanol at about 100°.[177] The product in this case is the ethyl ester.

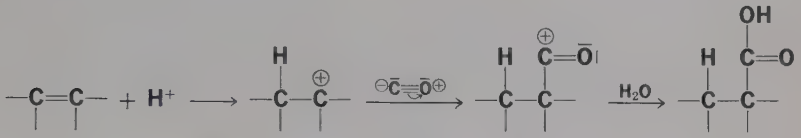
[173] Frank and Foster, *J. Org. Chem.* **26**, 303 (1961); Frank, Leebrick, Moormeier, Scheben, and Homberg, *J. Org. Chem.* **26**, 307 (1961).

[174] Baizer, *Tetrahedron Letters* **1963**, 973; Baizer and Anderson, *J. Org. Chem.* **30**, 1357 (1965); Anderson and Baizer, *Tetrahedron Letters* **1965**, 511.

[175] For reviews, see Olah and Olah, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 1272–1296, Interscience Publishers, Inc., New York, 1964; Bird, *Chem. Rev.* **62**, 283–302 (1962).

[176] Sternberg, Markby, and Wender, *J. Am. Chem. Soc.* **82**, 3638 (1960).

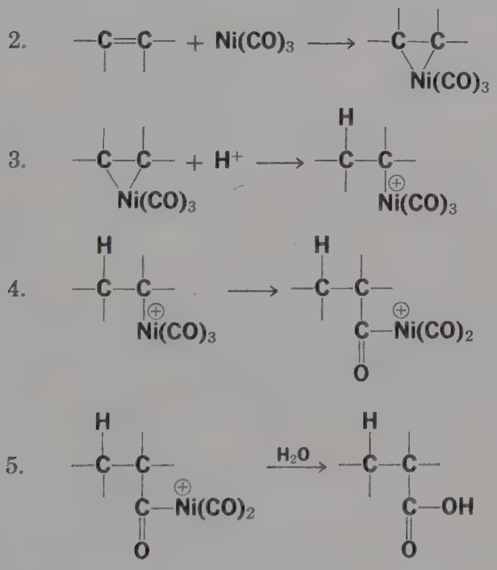
When acid catalysts are employed, in the absence of nickel carbonyl, the mechanism involves initial attack by a proton, followed by attack of the resulting carbonium ion on carbon monoxide to give an acylonium ion, which, with water, gives the product:



Therefore, Markovnikov's rule is followed. If alcohols, mercaptans, amines, etc., are used instead of water, then the acylonium ion combines with these, to give, respectively, esters, thiol esters, amides, etc., directly.

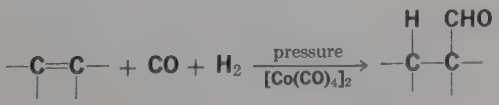
For the nickel carbonyl reaction, the addition is cis, for both alkenes and alkynes.[178] The following mechanism has been proposed:[178]

1. $Ni(CO)_4 \longrightarrow Ni(CO)_3 + CO$



Step 3 is an electrophilic substitution. The principal step of the mechanism, step 4, is a rearrangement.

5-19 Hydroformylation



$$-C{=}C- + CO + H_2 \xrightarrow[{[Co(CO)_4]_2}]{\text{pressure}} -\overset{H}{C}-\overset{CHO}{C}-$$

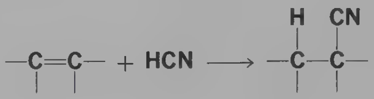
---

[177] Tsuji, Morikawa, and Kiji, *J. Am. Chem. Soc.* **86,** 4851 (1964); Tsuji, Kiji, Imamura, and Morikawa, *J. Am. Chem. Soc.* **86,** 4350 (1964).

[178] Bird, Cookson, Hudec, and Williams, *J. Chem. Soc.* **1963,** 410.

Olefins may be hydroformylated by treatment with carbon monoxide and hydrogen, over a catalyst which is usually a cobalt carbonyl but is sometimes another transition-metal compound.[179] Commercially, this is called the *oxo process,* but it may be carried out in the laboratory in an ordinary hydrogenation apparatus. Alcohols may be obtained by allowing the reduction to continue after all of the carbon monoxide is used up. It has been shown[180] that the formation of alcohols is a second step, occurring after the formation of aldehydes and that $HCo(CO)_3$ is the reducing agent.

5-20 Addition of HCN



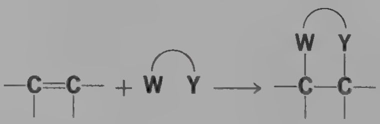
$$-\underset{|}{C}=\underset{|}{C}- + HCN \longrightarrow -\overset{H}{\underset{|}{C}}-\overset{CN}{\underset{|}{C}}-$$

Ordinary olefins do not react with HCN, but polyhalo olefins and olefins of the form C=C—Z add HCN to give nitriles.[181] The reaction is therefore a nucleophilic addition and is base-catalyzed. When Z is COR or, more especially, CHO, then 1,2 addition (reaction **6-49**, p. 711) is an important competing reaction and may be the only reaction. Triple bonds react very well, and one or two moles may be added, since the initial product is a Michael-type substrate. Acrylonitrile is commercially prepared in this way, by the addition of HCN to acetylene. HCN may be added to ordinary olefins in the presence of dicobalt octacarbonyl.[182]

OS **I,** 451; **II,** 498; **III,** 615; **IV,** 392, 393, 804; **40,** 11; **44,** 59.

5-21 Addition of ArH. See reaction **1-12** (p. 406) (Friedel-Crafts alkylation).

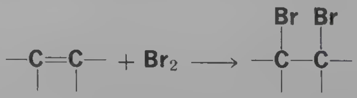
Reactions in Which Hydrogen Adds to Neither Side. Some of these reactions are *cycloadditions* (reactions **5-29, 5-30,** and **5-33** to **5-37**). In such cases addition to the multiple bond closes a ring:



$$-\underset{|}{C}=\underset{|}{C}- + \overset{\frown}{W\quad Y} \longrightarrow -\overset{\overset{\frown}{W\quad Y}}{\underset{|}{C}-\underset{|}{C}}-$$

A. Halogen on one or both sides

5-22 Halogenation of double and triple bonds (addition of halogen, halogen)



$$-\underset{|}{C}=\underset{|}{C}- + Br_2 \longrightarrow -\overset{Br}{\underset{|}{C}}-\overset{Br}{\underset{|}{C}}-$$

---

[179] For example, rhodium catalysts were used by Osborn, Wilkinson, and Young, *Chem. Commun.* **1965**, 17.

[180] Aldridge and Jonassen, *J. Am. Chem. Soc.* **85,** 886 (1963).

[181] For a review, see Mowry, *Chem. Rev.* **42,** 189–283 (1948).

[182] Arthur, England, Pratt, and Whitman, *J. Am. Chem. Soc.* **76,** 5364 (1954).

Most double bonds are easily halogenated with bromine, chlorine, or interhalogen compounds. Iodination has also been accomplished, but the reaction is slower.[183] Under free-radical conditions, iodination proceeds more easily.[184] However, *vic*-diiodides are generally unstable and tend to revert to iodine and the olefin. The order of activity for some of the reagents is $BrCl > Br_2 > ICl > IBr > I_2$.[185] Mixed halogenations have also been achieved by other methods. Mixtures of Br_2 and Cl_2 have been used to give bromochlorination;[186] iodofluorination has been accomplished with mixtures of KF and I_2;[187] and mixtures of N-bromo amides in anhydrous HF give bromofluorination.[188] Under ordinary conditions fluorine itself is too reactive to give simple addition; it attacks other bonds, and mixtures are obtained.[189] However, F_2 has been successfully added to certain double bonds in an inert solvent at low temperatures (−78°).[190] Addition of fluorine has also been accomplished with other reagents, for example, CoF_3[191] and a mixture of PbO_2 and SF_4.[192] XeF_4 has also been used for this purpose,[193] but isomerization takes place, so that ethylene gave 45% 1,2-difluoroethane, but also 35% of the 1,1-difluoro isomer. With perfluoroethylene, where isomerization is not a factor, XeF_4 gave good yields of the normal addition product.

The reaction with bromine is very rapid and is easily carried out at room temperature. Bromine is often used as a test, qualitative or quantitative, for unsaturation.[194] The vast majority of double bonds can be successfully brominated. Even when aldehyde, ketone, amine, etc., functions are present in the molecule, they do not interfere, since the reaction with double bonds is faster.

The mechanism is usually electrophilic (see p. 565), but when free-radical initiators (or ultraviolet light) are present, then addition may occur by a free-radical mechanism.[195] Once Br· or Cl· radicals are formed, however, then substitution may compete (reaction **4-1**, p. 532, and reaction **4-2**, p. 535). This is especially important when the olefin has allylic hydrogens. Under free-radical conditions (ultraviolet light) bromine or chlorine adds to the benzene ring to give, respectively, hexabromo- and hexachlorocyclohexane. Fluorine also adds to benzene, but the result is a mixture of addition and substitution products. For example, octafluoro-, nonafluoro-, and decafluorocyclohexanes are among the products.[196]

[183] Sumrell, Wyman, Howell, and Harvey, *Can. J. Chem.* **42**, 2710 (1964).

[184] Skell and Pavlis, *J. Am. Chem. Soc.* **86**, 2956 (1964).

[185] White and Robertson, *J. Chem. Soc.* **1939**, 1509.

[186] Buckles, Forrester, Burham, and McGee, *J. Org. Chem.* **25**, 24 (1960).

[187] Kreespan, *J. Org. Chem.* **27**, 1813 (1962).

[188] Robinson, Finckenor, Oliveto, and Gould, *J. Am. Chem. Soc.* **81**, 2191 (1959); Bowers, *J. Am. Chem. Soc.* **81**, 4107 (1959); Pattison, Peters, and Dean, *Can. J. Chem.* **43**, 1689 (1965).

[189] See, for example, Fuller, Stacey, Tatlow, and Thomas, *Tetrahedron* **18**, 123 (1962).

[190] Merritt and Stevens, *J. Am. Chem. Soc.* **88**, 1822 (1966).

[191] Rausch, Davis, and Osborne, *J. Org. Chem.* **28**, 494 (1963).

[192] Bissell and Fields, *J. Org. Chem.* **29**, 1591 (1964).

[193] Shieh, Yang, and Chernick, *J. Am. Chem. Soc.* **86**, 5021 (1964).

[194] For a review of this, see Kuchar, in Patai, "The Chemistry of Alkenes," pp. 273–280, Interscience Publishers, Inc., New York, 1964.

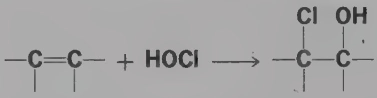
[195] For example, see Poutsma, *J. Am. Chem. Soc.* **87**, 2161, 2172 (1965). For a review of the mechanisms of halogen addition, see de la Mare, Ref. 40.

[196] Smith and Tatlow, *J. Chem. Soc.* **1957**, 2505; Stephens, Tatlow, and Wiseman, *J. Chem. Soc.* **1959**, 148–158; Nield, Stephens, and Tatlow, *J. Chem. Soc.* **1959**, 159.

Conjugated systems give both 1,2 and 1,4 addition.[197] Triple bonds add bromine, but more slowly than double bonds. Molecules that contain both double and triple bonds are preferentially attacked at the double bond. Two moles of bromine may be added to triple bonds to give tetrabromo products. There is evidence that the addition of the first mole of bromine to a triple bond may take place by a nucleophilic mechanism.[198] With allenes it is very easy to stop the reaction after only one mole has added, to give X—C—CX=C. In most cases a second mole of halogen can be added only by forced treatment. Addition of halogen to ketenes gives α-halo acyl halides, but the yields are not good. When bromine was added to *cis*- and *trans*-cyclodecenes, the products were, respectively, *cis*- and *trans*-1,6-dibromocyclodecane.[199] In this case there was a transannular hydride shift.

OS **I**, 205, 521; **II**, 171, 177, 270, 408; **III**, 105, 123, 127, 209, 350, 526, 531, 731, 785; **IV**, 130, 195, 748, 851, 969; **40**, 29; **45**, 86; **46**, 10, 34.

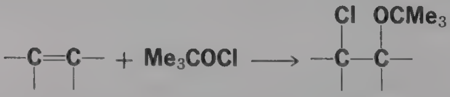
5-23 Addition of hypohalous acids and hypohalites (addition of halogen, oxygen)



$$-\underset{|}{C}=\underset{|}{C}- + \text{HOCl} \longrightarrow -\underset{|}{\overset{\text{Cl}}{\overset{|}{C}}}-\underset{|}{\overset{\text{OH}}{\overset{|}{C}}}-$$

HOCl, HOBr, and HOI may be added to olefins to produce halohydrins. Fluorohydrins have been prepared by treatment with OF_2 at −78°, but this is not a general method.[200] The direct product in this case is $F-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-OF$, which is not isolated, but converted to the fluorohydrin. Unfortunately it is converted to other products, too. The mechanism of HOX addition is electrophilic, with initial attack by the positive halogen end of the HOX dipole. Following Markovnikov's rule, the positive halogen goes to the side of the double bond which has more hydrogens. The resulting carbonium ion (or bromonium or iodonium ion) reacts with OH^- or H_2O to give the product. At least with HOBr and HOCl, the addition is trans.[201] If the addition is performed in an alcohol or a carboxylic acid solvent, then it is possible to obtain, directly, $X-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-OR$ or $X-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-OCOR$, respectively (also see reaction **5-28**). HOCl and HOBr may be added to triple bonds to give dihalo carbonyl compounds $-CX_2-CO-$.

tert-Butyl hypochlorite adds to double bonds to give *tert*-butyl ethers:[202]



$$-\underset{|}{C}=\underset{|}{C}- + \text{Me}_3\text{COCl} \longrightarrow -\underset{|}{\overset{\text{Cl}}{\overset{|}{C}}}-\underset{|}{\overset{\text{OCMe}_3}{\overset{|}{C}}}-$$

---

[197] For a review, see Cais, in Patai, "The Chemistry of Alkenes," pp. 993–999, Interscience Publishers, Inc., New York, 1964.

[198] Sinn, Hopperdietzel, and Sauermann, *Monatsh. Chem.* **96**, 1036 (1965).

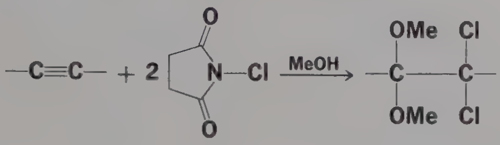
[199] Závada and Sicher, *Proc. Chem. Soc.* **1961**, 199.

[200] Merritt and Ruff, *J. Org. Chem.* **30**, 328 (1965).

[201] Collis and Merrall, *Chem. Ind.* (*London*) **1964**, 711.

[202] For a review, see Anbar and Ginsburg, *Chem. Rev.* **54**, 925–958 (1954), pp. 929–933.

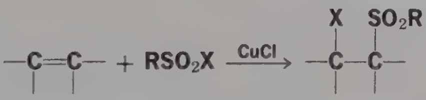
This is a convenient method for the preparation of tertiary ethers. Me_3COCl adds 1,2 to some conjugated dienes[202] and 1,4 to others.[203] When Me_3COCl is added to olefins in the presence of excess ROH, then the ether produced is $Cl{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}OR$.[204] Vinyl ethers give β-halo acetals.[205] Two moles of "MeOCl" can be added to triple bonds by treatment with N-chlorosuccinimide in methanol:[206]



These acetals may then be hydrolyzed to α,α-dichloro ketones.

OS **I,** 158; **IV,** 130, 157.

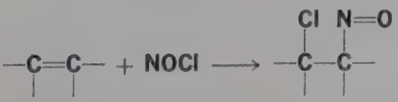
5-24 Addition of sulfur compounds (addition of halogen, sulfur)



$$-\underset{|}{C}{=}\underset{|}{C}- + RSO_2X \xrightarrow{CuCl} -\overset{X}{\underset{|}{\overset{|}{C}}}-\overset{SO_2R}{\underset{|}{\overset{|}{C}}}-$$

Sulfonyl halides add to double bonds, to give β-halo sulfones, in the presence of free-radical initiators. A particularly good catalyst is cuprous chloride.[207] In a similar reaction, sulfenyl chlorides, RSCl, give β-halo thioethers, $Cl{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}SR$. The latter may be free-radical or electrophilic additions, depending on conditions. Other sulfur compounds also add to double bonds by free-radical mechanisms.[208]

5-25 Addition of NOCl and related compounds (addition of halogen, nitrogen)



$$-\underset{|}{C}{=}\underset{|}{C}- + NOCl \longrightarrow -\overset{Cl}{\underset{|}{\overset{|}{C}}}-\overset{N{=}O}{\underset{|}{\overset{|}{C}}}-$$

There are three possible products when NOCl is added to olefins.[209] The initial product is always the β-halo nitroso compound, but these are stable only if the carbon bearing the nitrogen has no hydrogen. If it has, the nitroso compound tautomerizes to the oxime:

---

[203] Riemschneider and Nehring, *Ann.* **660,** 41 (1962).

[204] Geneste and Kergomard, *Bull. Soc. chim. France* **1963,** 470.

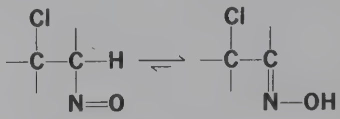
[205] Weissermel and Lederer, *Chem. Ber.* **96,** 77 (1963).

[206] Reed, *J. Org. Chem.* **30,** 2195 (1965).

[207] Asscher and Vofsi, *J. Chem. Soc.* **1964,** 4962.

[208] For reviews, see Stacey and Harris, *Org. Reactions* **13,** 150–376 (1963), pp. 200–207, 327–332; Sosnovsky, Ref. 168, pp. 103–115; Walling, Ref. 168, pp. 326–332.

[209] For reviews, see Beckham, Fessler, and Kise, *Chem. Rev.* **48,** 319–396 (1951); Sosnovsky, Ref. 168, pp. 247–251, 272–275.



$$-\overset{Cl}{\underset{|}{\overset{|}{C}}}-\underset{N=O}{\underset{|}{\overset{|}{C}}}-H \rightleftharpoons -\overset{Cl}{\underset{|}{\overset{|}{C}}}-\underset{N-OH}{\underset{\|}{\overset{|}{C}}}$$

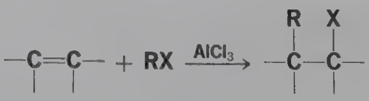
With simple olefins, the initial β-halo nitroso compound is oxidized by the NOCl to a β-halo nitro compound. Many functional groups may be present without interference, for example, COOH, COOR, CN, OR, etc. In the past, the reaction was invaluable in the characterization of terpenes. The mechanism in most cases is probably simple electrophilic addition, and the addition is usually trans, although cis addition has been reported in some cases.[210] The stereochemistry of the product can be controlled, at least in some cases, by choice of a suitable solvent. For example, the addition to cyclohexene was trans in liquid SO_2 and cis in trichloroethylene.[211] Markovnikov's rule is followed, with the positive NO going to the carbon which has more hydrogens.

Nitryl chloride (NO_2Cl) also adds to olefins, to give β-halo nitro compounds, but this is a free-radical process. The NO_2 goes to the less substituted carbon.[212] Nitryl chloride also adds to triple bonds to give the expected 1-nitro-2-chloro olefins.[213] β-Halo nitro compounds can also be prepared by treatment of olefins with N_2O_4 and bromine (or iodine), but another possible product is the β-halo nitrate.[214] Which product is formed depends on the substrate. FNO_2 can be added to olefins by treatment with HF in HNO_3.[215]

When olefins are treated with NaN_3, $FeCl_3$, $FeSO_4$, and H_2O_2, β-chloro azides, $Cl-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-N_3$, are formed, in a free-radical process.[216] In another free-radical reaction, N-halo secondary amines, R_2NCl, add to olefins, allenes, conjugated dienes, and alkynes to give addition of R_2N and Cl.[217]

OS **IV,** 711; **45,** 74.

5-26 Addition of alkyl halides (addition of halogen, carbon)



$$-\underset{|}{C}=\underset{|}{C}- + RX \xrightarrow{AlCl_3} -\underset{|}{\overset{R}{\overset{|}{C}}}-\underset{|}{\overset{X}{\overset{|}{C}}}-$$

---

[210] For example, see Meinwald, Meinwald, and Baker, *J. Am. Chem. Soc.* **86,** 4074 (1964).

[211] Ohno, Okamoto, and Nukada, *Tetrahedron Letters* **1965,** 4047.

[212] Shechter, *Record Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) **25,** 55–76 (1964).

[213] Schlubach and Braun, *Ann.* **627,** 28 (1959).

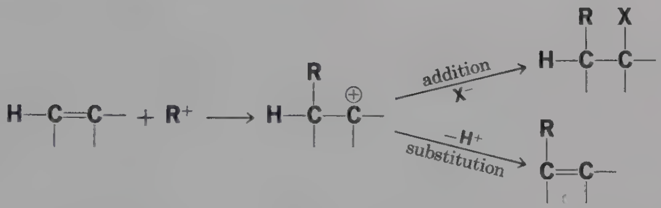
[214] Bachman, Logan, Hill, and Standish, *J. Org. Chem.* **25,** 1312 (1960).

[215] Knunyants, German, and Rozhkov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963,** 1794.

[216] Minisci and Galli, *Tetrahedron Letters* **1963,** 357.

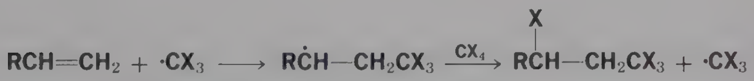
[217] Neale and Hinman, *J. Am. Chem. Soc.* **85,** 2666 (1963); Neale, *J. Am. Chem. Soc.* **86,** 5340 (1964), *Tetrahedron Letters* **1966,** 483; Minisci, Galli, and Cecere, *Tetrahedron Letters* **1966,** 3163.

Alkyl halides may be added to olefins in the presence of a Friedel-Crafts catalyst, most often $AlCl_3$.[218] The yields are best for tertiary R. Secondary R may also be used, but primary R give rearrangement products (as with reaction **1-12**, p. 406). Methyl and ethyl halides, which cannot rearrange, give no reaction at all. The attacking species is the carbonium ion formed from the alkyl halide and the catalyst (see reaction **1-12**). The addition therefore follows Markovnikov's rule, with the carbonium ion going to the carbon with more hydrogens. Substitution is a side reaction, arising from loss of hydrogen from the carbonium ion formed when the original carbonium ion attacks the double bond:



Conjugated dienes can add 1,4.[219] Triple bonds react, but less readily, and give lower yields because of side reactions.

CCl_4, $BrCCl_3$, ICF_3, and similar simple polyhalo alkanes add to olefins in good yield.[220] These are free-radical additions and require initiation by peroxides or ultraviolet light. The initial attack is by the carbon, and it goes to the carbon which has more hydrogens, as in most free-radical attack:



$$RCH{=}CH_2 + \cdot CX_3 \longrightarrow R\dot{C}H{-}CH_2CX_3 \xrightarrow{CX_4} R\overset{X}{C}H{-}CH_2CX_3 + \cdot CX_3$$

This type of polyhalo alkane adds to halogenated olefins in the presence of $AlCl_3$ by an electrophilic mechanism.[221] This is called the *Prins reaction* (not to be confused with the other Prins reaction, **6-51**, p. 711).

ArX can be added across double bonds, in a free-radical process, by treatment of olefins with diazonium salts, but Meerwein arylation (substitution) (reaction **4-16**, p. 552) competes.[222] This addition may be either 1,2 or 1,4 with conjugated dienes.[223]

OS **II**, 312; **IV**, 727; **45**, 104.

---

[218] For a review, see Schmerling, in Olah, "Friedel-Crafts and Related Reactions," vol. 2, pp. 1133–1174, Interscience Publishers, Inc., New York, 1963.

[219] Kolyaskina and Petrov, *J. Gen. Chem. USSR* **32**, 1067 (1962).

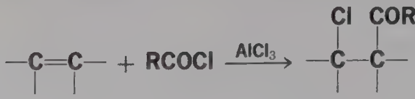
[220] For reviews, see Walling and Huyser, *Org. Reactions* **13**, 91–149 (1963), pp. 107–108, 122–131; Sosnovsky, Ref. 168, pp. 19–61; Walling, Ref. 168, pp. 247–272.

[221] Ref. 218, pp. 1150, 1162.

[222] Iurkevich, Dombrovskii, and Terent'ev, *J. Gen. Chem. USSR* **28**, 226 (1958).

[223] Dombrovskii and Ganushchak, *J. Gen. Chem. USSR* **31**, 1191 (1961), **32**, 1867 (1962); Ganushchak, Yukhomenko, Stadnichuk, and Dombrovskii, *J. Gen. Chem. USSR* **34**, 2249 (1964).

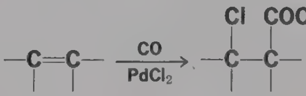
5-27 Addition of acyl halides (addition of halogen, carbon)



$$-\underset{|}{C}=\underset{|}{C}- + RCOCl \xrightarrow{AlCl_3} -\underset{|}{\overset{\overset{Cl}{|}}{C}}-\underset{|}{\overset{\overset{COR}{|}}{C}}-$$

Acyl halides have been added to many olefins, in the presence of Friedel-Crafts catalysts. The reaction has been applied to straight-chain, branched, and cyclic olefins, but to very few containing functional groups, except halogen.[224] The mechanism is similar to that of reaction **5-26,** and, as in that case, substitution competes (see reaction **2-9,** p. 463). Increasing temperature favors substitution,[225] and good yields of addition can be realized if the temperature is kept under 0°. The reaction usually fails with conjugated dienes, since polymerization predominates. The reaction may be performed on triple-bond compounds, producing compounds of the form $RCO-\underset{|}{C}=\underset{|}{C}-Cl$.[226] A *formyl* group and a halogen may be added to triple bonds by treatment with N,N-disubstituted formamides and $POCl_3$ (Vilsmeier conditions, see reaction **1-18,** p. 417).[227]

When olefins are treated with carbon monoxide in the presence of $PdCl_2$, β-chloro acyl halides are produced:[228]



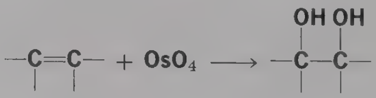
$$-\underset{|}{C}=\underset{|}{C}- \xrightarrow[PdCl_2]{CO} -\underset{|}{\overset{\overset{Cl}{|}}{C}}-\underset{|}{\overset{\overset{COCl}{|}}{C}}-$$

though not in high yield. The carbon goes to the side with more hydrogens.

OS **IV,** 186.

B. Oxygen or nitrogen on one or both sides

5-28 Hydroxylation (addition of oxygen, oxygen)



$$-\underset{|}{C}=\underset{|}{C}- + OsO_4 \longrightarrow -\underset{|}{\overset{\overset{OH}{|}}{C}}-\underset{|}{\overset{\overset{OH}{|}}{C}}-$$

There are many reagents which add two OH groups to a double bond.[229] OsO_4 and alkaline $KMnO_4$ give cis addition, from the less hindered side of the double bond. Osmium tetroxide adds rather slowly, but almost quantitatively. The cyclic ester **52** is an intermediate and can be isolated, but is usually decomposed in solution, with sodium sulfite in ethanol or other reagents. Bases catalyze the reaction by coordinating with the ester. The chief drawback to this reaction is that OsO_4 is expensive and highly toxic, so that its use has been limited to small-scale preparations of scarce materials. Cis addition may also be accomplished by use of H_2O_2 with OsO_4 present in catalytic amounts.

---

[224] For a review, see Nenitzescu and Balaban, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 1033–1152, Interscience Publishers, Inc., New York, 1964.

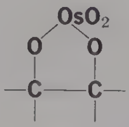
[225] Jones, Taylor, and Rudd, *J. Chem. Soc.* **1961,** 1342.

[226] For example, see Nifant'ev, Grachev, Bakinovskii, Kara-Murza, and Kochetkov, *J. Appl. Chem. USSR* **36,** 646 (1963).

[227] Yen, *Ann. chim.* (*Paris*) [13] **7,** 785 (1962).

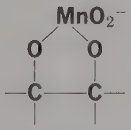
[228] Tsuji, Morikawa, and Kiji, *J. Am. Chem. Soc.* **86,** 4851 (1964).

[229] For a review, see Gunstone, *Advan. Org. Chem.* **1,** 103–147 (1960).



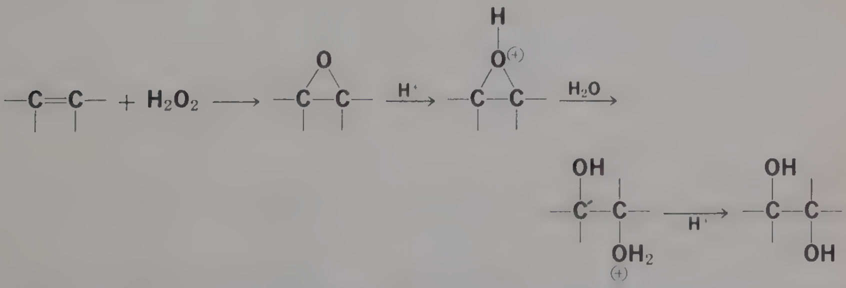
52

Potassium permanganate is a strong oxidizing agent and can oxidize the glycols which are the products of this reaction (see reactions **9-8**, p. 867, and **9-11**, p. 875). In acid and neutral solution it always does so; hence it is not feasible to prepare glycols in this manner. Glycols may be prepared with alkaline permanganate, but the conditions must be mild. Even so, yields are seldom above 50%. As with OsO_4, it is likely that a cyclic ester (**53**) is an intermediate. This reaction is the basis of the *Baeyer test* for the presence of double bonds.



53

Trans hydroxylation may be achieved by treatment with H_2O_2 and formic acid. In this case, epoxidation (reaction **5-29**) occurs first, followed by an S_N2 reaction, resulting in overall trans addition:



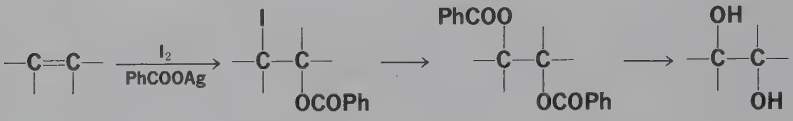
The same result can be achieved in one step with monopersuccinic acid.[230] Overall trans addition may also be achieved by the method of Prevost.[231]

---

[230] Lombard and Schroeder, *Bull. Soc. chim. France* **1963**, 2800.

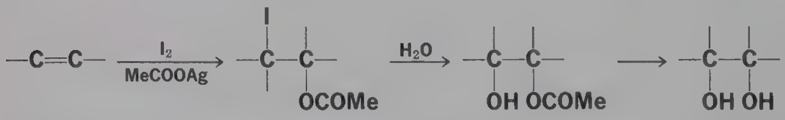
[231] For reviews of Prevost's and Woodward's methods, see Wilson, *Org. Reactions* **9**, 332–387 (1957), pp. 350–352.

In this method the olefin is treated with iodine and silver benzoate in a 1:2 molar ratio. The initial addition is trans and results in a β-halo benzoate (**54**). These can be isolated, and this represents a method of addition of IOCOPh. However, under the normal reaction conditions, the iodine is replaced by a second PhCOO group. This is a nucleophilic substitution reaction, and it operates by the neighboring-group mechanism (p. 263), so that the groups are still trans:



54

Hydrolysis of the ester does not change the configuration. The method of Woodward is similar, but results in overall cis hydroxylation. The olefin is treated with iodine and silver acetate in a 1:1 molar ratio (with excess silver acetate, the Hunsdiecker reaction, **4-26,** p. 559, occurs). Here again, the initial product is a β-halo ester; the addition is trans; and a nucleophilic replacement of the iodine occurs. However, in the presence of water as solvent, neighboring-group participation is prevented or greatly decreased by solvation of the ester function, and the mechanism is the normal S_N2 process, so that the monoacetate is cis. Hydrolysis gives the *cis*-glycol:

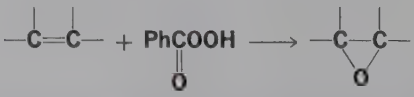


Although the Woodward method results in overall cis addition, the product may be different from that with OsO_4 or $KMnO_4$, since the overall cis process is from the more hindered side of the olefin. Addition of IOCOMe has also been accomplished with iodine and peracetic acid.[232]

Olefins may also be oxidized with metallic acetates such as lead tetraacetate or thallium acetate to give bis-acetates of glycols.[233]

OS **II,** 307; **III,** 217; **IV,** 317; **41,** 53.

5-29 Epoxidation (addition of oxygen, oxygen)



Olefins may be epoxidated with any of a number of peracids, of which perbenzoic is the most often used. The reaction has wide utility.[234] Alkyl, aryl, hydroxyl, ester, and other groups may be present, though not amino groups, since these are affected by the reagent. When the substrate is an α,β-unsaturated ester, then the product is a glycidic ester.[235] Electron-donating groups increase the rate, and the reaction is particularly rapid with tetraalkylolefins. Conditions are mild, and yields are high. Other peracids, especially peracetic, are also used; trifluoroperacetic acid is a particularly good one. Occasionally the reaction is performed with H_2O_2 and a carboxylic acid, so that the peracid is generated *in situ*. Glycols and glycol esters (reaction **5-28**) are side products.

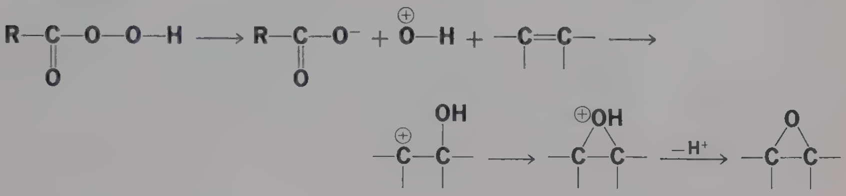
---

[232] Ogata and Aoki, *J. Org. Chem.* **31,** 1625 (1966).

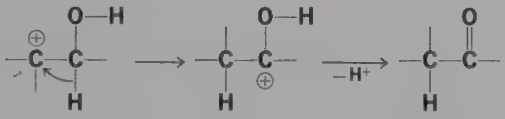
[233] For example, see Anderson and Winstein, *J. Org. Chem.* **28,** 605 (1963).

[234] For reviews, see Swern, *Org. Reactions* **7,** 378–433 (1953); House, "Modern Synthetic Reactions," pp. 109–123, W. A. Benjamin, Inc., New York, 1965.

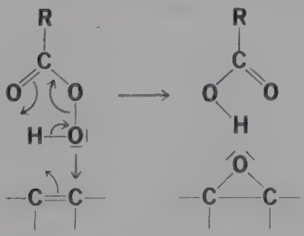
One mechanism proposed for the reaction involves attack by OH^+, formed by ionization of the peracid:[236]



This accounts for ketones often found as side products:[237]



However, a mechanism which has won greater acceptance involves the simultaneous happening of all four of the above steps:[238]



Evidence for the latter mechanism is:[239] (1) The reaction is second order. If ionization were the rate-determining step, it would be first order in peracid. (2) The reaction readily takes place in nonpolar solvents, where formation of ions is inhibited. (3) The addition is stereospecific. That is, a trans olefin gives a trans epoxide, and a cis olefin a cis epoxide:

---

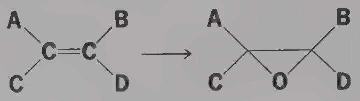
[235] MacPeek, Starcher, and Phillips, *J. Am. Chem. Soc.* **81**, 680 (1959).

[236] Weisenborn and Taub, *J. Am. Chem. Soc.* **74**, 1329 (1952).

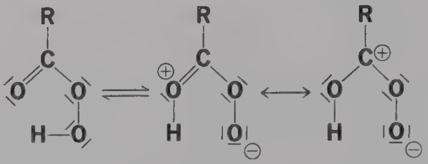
[237] Filler, Camara, and Naqvi, *J. Am. Chem. Soc.* **81**, 658 (1959).

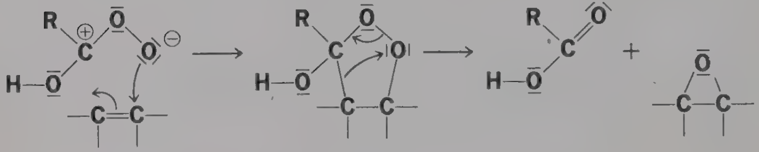
[238] Bartlett, *Record Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) **18**, 111 (1957).

[239] Ogata and Tabushi, *J. Am. Chem. Soc.* **83**, 3440 (1961).



Another mechanism, postulated more recently, is also in accord with the above facts:[240]





The key step of this mechanism is the 1,3-dipolar addition (see reaction **5-33**) of a tautomer of the peroxy acid. The five-membered cyclic adduct then rearranges to the products. Evidence against the 1,3-dipolar mechanism has been reported by Bingham and coworkers,[240a] who found that the rates of epoxidation of cyclohexene and norbornene by perlauric acid were approximately the same, though in typical 1,3-dipolar additions norbornene reacts 10^3 to 10^4 times faster than cyclohexene.

Conjugated dienes may be epoxidized (1,2 addition), though the reaction is slower than for corresponding olefins, but α,β-unsaturated ketones react very slowly or not at all. When a carbonyl group is in the molecule, but not conjugated with the double bond, then the Baeyer-Villiger reaction (**8-20**, p. 822) may compete. It has been shown that 2-allylcyclohexanone, treated with peracetic acid, gives the Baeyer-Villiger reaction, but with H_2O_2 and benzonitrile, gives epoxidation.[241]

α,β-Unsaturated ketones (including quinones) and aldehydes may be epoxidated with alkaline H_2O_2,[242] but this is a nucleophilic addition by a Michael-type mechanism, involving attack by HO_2^-:[243]

---

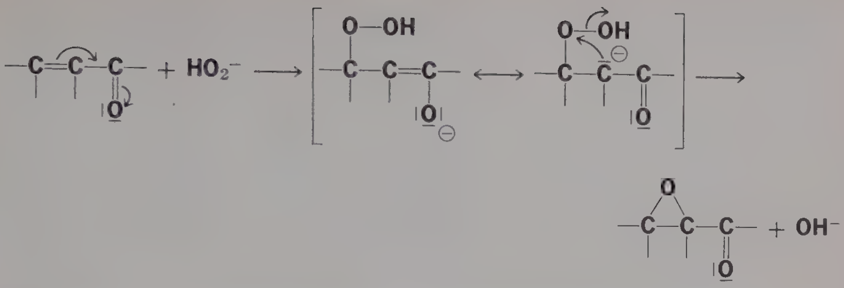
[240] Kwart and Hoffman, *J. Org. Chem.* **31**, 419 (1966).

[240a] Bingham, Meakins, and Whitham, *Chem. Commun.* **1966**, 445. See, however, Kwart, Starcher, and Tinsley, *Chem. Commun.* **1967**, 335.

[241] Payne, *Tetrahedron* **18**, 763 (1962).

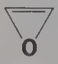
[242] For example, see Payne and Williams, *J. Org. Chem.* **24**, 54 (1959), **26**, 651 (1961).

[243] Bunton and Minkoff, *J. Chem. Soc.* **1949**, 665. For a review, see Patai and Rappoport, in Patai, "The Chemistry of Alkenes," pp. 512–517, Interscience Publishers, Inc., New York, 1964.



Epoxides may also be prepared by treating olefins with oxygen. This is probably a free-radical process.[244]

It would be useful if triple bonds could be simply epoxidated to give oxirenes (**55**). However, oxirenes are unknown. They probably form in the

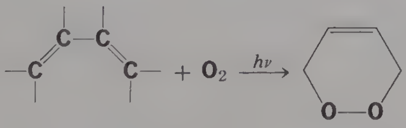


55

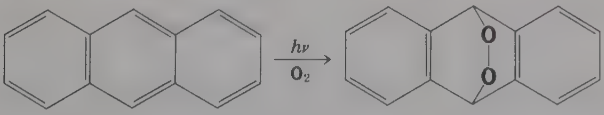
reaction[245] but react further before they can be isolated.

OS **I,** 494; **IV,** 552, 860; **42,** 50.

5-30 Photooxidation of dienes (addition of oxygen, oxygen)



Conjugated dienes react with oxygen under the influence of light to give internal peroxides.[246] The reaction has mostly been applied to cyclic dienes. The scope extends to certain aromatic compounds, e.g.,



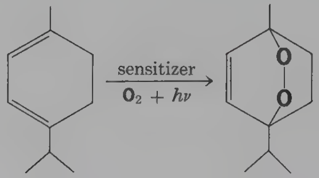
In addition to those dienes and aromatic rings which may be photooxidized directly, there is a larger group which give the reaction in the presence of a photosensitizer such as eosin. Among these is α-terpinene, which is converted to ascaridole:

---

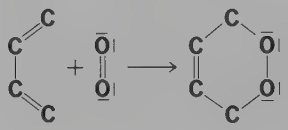
[244] Brill, *J. Am. Chem. Soc.* **85,** 141 (1963); Moss and Steiner, *J. Chem. Soc.* **1965,** 2372; Sérée de Roch, *Bull. Soc. chim. France* **1965,** 1979.

[245] McDonald and Schwab, *J. Am. Chem. Soc.* **86,** 4866 (1964); Stille and Whitehurst, *J. Am. Chem. Soc.* **86,** 4871 (1964).

[246] For reviews, see Arbuzov, *Russ. Chem. Rev.* **34,** 558–574 (1965); and Walling, "Free Radicals in Solution," pp. 453–457, John Wiley & Sons, Inc., New York, 1957.



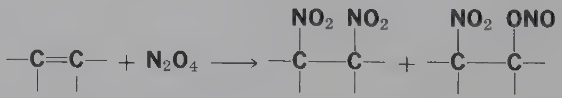
At first it may seem strange that oxygen, which is a diradical, needs photosensitization, either by light or a photosensitizer, to cause it to add to the conjugated system. But it has been shown that it is not the ground-state oxygen (the triplet) which reacts, and that the purpose of the photosensitization is to elevate the oxygen to an excited state in which it is a singlet (i.e., all electrons are paired), so that the reaction is actually a Diels-Alder reaction (see **5-34**) with oxygen as dienophile:[247]



Like reaction **5-34**, this reaction is reversible.

5-31 Addition of aldehydes and ketones (addition of carbon, oxygen). See the Prins reaction (**6-51**, p. 711) and reactions **6-52** (p. 713), **6-65** (p. 723), and **6-66** (p. 724).

5-32 Addition of N_2O_4 and related reactions (addition of nitrogen, nitrogen or nitrogen, oxygen):



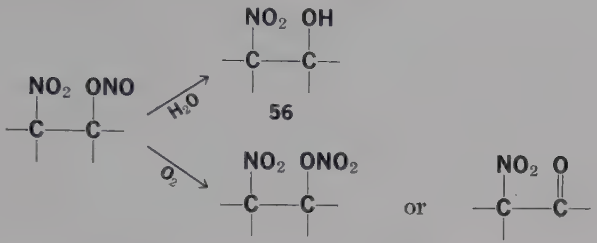
$$-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}- + N_2O_4 \longrightarrow -\overset{NO_2}{\underset{|}{\overset{|}{C}}}-\overset{NO_2}{\underset{|}{\overset{|}{C}}}- + -\overset{NO_2}{\underset{|}{\overset{|}{C}}}-\overset{ONO}{\underset{|}{\overset{|}{C}}}-$$

When olefins are treated with N_2O_4 in an ether or ester as solvent, *vic*-dinitro compounds and β-nitro alkyl nitrites are produced.[248] The reaction may be successfully performed with all kinds of olefins and acetylenes. Generally, both products are produced. The dinitro compound is usually stable, but the ester is quite reactive. Upon addition of water or alcohol it is hydrolyzed to a β-nitro alcohol. If oxygen is added, it is oxidized to a β-nitro alkyl nitrate, or an α-nitro aldehyde or ketone.

---

[247] Foote and Wexler, *J. Am. Chem. Soc.* **86**, 3880 (1964); Corey and Taylor, *J. Am. Chem. Soc.* **86**, 3881 (1964); Foote, Wexler, and Ando, *Tetrahedron Letters* **1965**, 4111.

[248] For reviews, see Stacey and Harris, *Org. Reactions* **13**, 150–376 (1963), pp. 224–229, 361–367; Shechter, *Record Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) **25**, 55–76 (1964); Noble, Borgardt, and Reed, *Chem. Rev.* **64**, 19–57 (1964), pp. 20–22; Sosnovsky, Ref. 168, pp. 252–269.

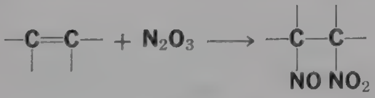


The nitrate is stable. Even without deliberate addition of oxygen, it is not uncommon to find some nitrate or ketone. It is therefore possible to prepare four types of compound in this reaction, not counting the nitrite.

The mechanism is probably of the free-radical type,[249] with initial attack by NO_2 to give $-\underset{\cdot}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-NO_2$ as the intermediate for both products. In accord with this, the nitro group (in the nitrite derivatives) is found on the side with more hydrogens.

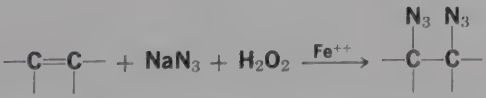
β-Nitro alcohols (**56**) may also be prepared indirectly, by addition of acetyl nitrate ($AcONO_2$) to double bonds.[250] The resulting β-nitro acetate may be hydrolyzed to the alcohol. Side products of the addition of $AcONO_2$ are nitro olefins. The addition follows Markovnikov's rule, with the nitro group going to the carbon with more hydrogens.

N_2O_3 adds to olefins to give β-nitroso nitro compounds:



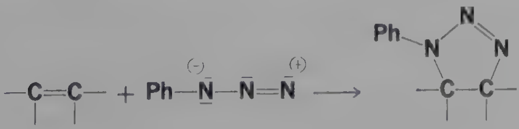
$$-C{=}C- + N_2O_3 \longrightarrow -\underset{NO}{C}-\underset{NO_2}{C}-$$

Two azide groups may be added to double bonds by treatment with sodium azide and hydrogen peroxide, in the presence of ferrous ion:[251]



$$-C{=}C- + NaN_3 + H_2O_2 \xrightarrow{Fe^{++}} -\overset{N_3}{C}-\overset{N_3}{C}-$$

5-33 1,3-Dipolar addition (addition of oxygen, nitrogen, carbon)



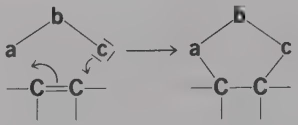
---

[249] Shechter, Gardikes, and Pagano, *J. Am. Chem. Soc.* **81,** 5420 (1959).

[250] Bordwell and Garbisch, *J. Am. Chem. Soc.* **82,** 3588 (1960), *J. Org. Chem.* **27,** 2322, 3049 (1962), **28,** 1765 (1963).

[251] Minisci and Galli, *Tetrahedron Letters* **1962,** 533.

Azides add to double bonds to give triazolines. This is one example of a large group of reactions (2 + 3 cycloadditions) in which five-membered heterocyclic compounds are prepared by addition to double bonds of 1,3-dipolar compounds.[252] These are compounds which have a sequence of three atoms a—b—c, of which a has a sextet of electrons in the outer shell, and c an octet with at least one unshared pair. The reaction may then be formulated as



Since compounds with six electrons in the outer shell of an atom are usually not stable, the a—b—c system is actually one canonical structure of a resonance hybrid, for which at least one other structure may be drawn, e.g., for azides

$$R-\overset{\ominus}{\underline{\bar{N}}}-\bar{N}=\overset{\oplus}{\bar{N}} \longleftrightarrow R-\overset{\ominus}{\underline{\bar{N}}}-\overset{\oplus}{N}\equiv\bar{N}$$

1,3-Dipolar compounds may be divided into two main types:

1. Those in which the dipolar canonical form has a double bond on the sextet atom, and the other canonical form a triple bond on that atom:

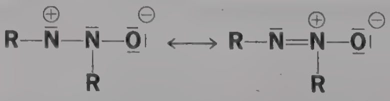
$$-\overset{\oplus}{a}=\underline{b}-\overset{\ominus}{\underline{c}} \longleftrightarrow -a\equiv\overset{\oplus}{b}-\overset{\ominus}{\underline{c}}$$

If we limit ourselves to the first row of the periodic table, b can only be nitrogen, a can be carbon or nitrogen, and c can be carbon, oxygen, or nitrogen; hence there are six types which fit this description. Among these are azides (a = b = c = N), illustrated above, and diazoalkanes $(R_2\overset{\ominus}{\bar{C}}-\bar{N}=\overset{\oplus}{\bar{N}})$.

2. Those in which the dipolar canonical form has a single bond on the sextet atom, and the other form a double bond:

$$-\overset{\oplus}{a}-\underline{b}-\overset{\ominus}{\underline{c}} \longleftrightarrow -a=\overset{\oplus}{b}-\overset{\ominus}{\underline{c}}$$

Here b can be nitrogen or oxygen, and a and c can be nitrogen, oxygen, or carbon, but there are only twelve types, since, for example, N—C—C is only another canonical form of C—C—N. Examples are azoxy compounds:



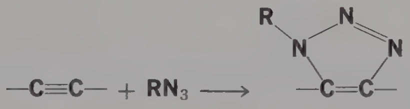
$$R-\overset{\oplus}{\bar{N}}-\underset{\substack{|\\R}}{\bar{N}}-\overset{\ominus}{\underline{\bar{O}}}| \longleftrightarrow R-\bar{N}=\underset{\substack{|\\R}}{\overset{\oplus}{N}}-\overset{\ominus}{\underline{\bar{O}}}|$$

---

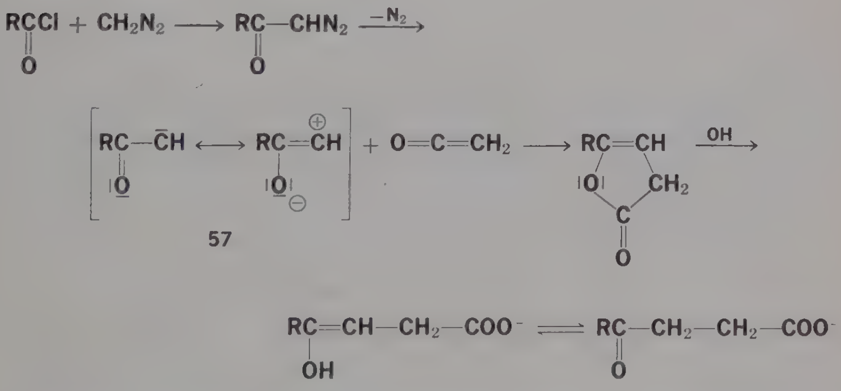
[252] For reviews, see Huisgen, *Angew. Chem. Intern. Ed. Engl.* **2**, 565–598, 633–645 (1963); *Proc. Chem. Soc.* **1961**, 357–369; Huisgen, Grashey, and Sauer, in Patai, "The Chemistry of Alkenes," pp. 806–878, Interscience Publishers, Inc., New York, 1964.

Of the eighteen systems, some of which are unstable and must be generated *in situ,* the reaction has been accomplished for at least fourteen, though not in all cases with a carbon-carbon double bond (the reaction also can be carried out with other double bonds). Not all olefins undergo 1,3-dipolar addition equally well. The reaction is most successful for those which are good dienophiles in the Diels-Alder reaction (**5-34**). The addition is stereoselective and cis, and the mechanism is probably a one-step synchronous process, as illustrated above. As expected for this type of mechanism, the rates do not vary much with changes in solvent.

Carbon-carbon triple bonds may also undergo 1,3-dipolar addition. For example, azides give triazoles:



The 1,3-dipolar addition to ketene of a carbene derived from a diazo ketone provides a method of increasing the length of a carbon chain by three:[253]


57

The first step is an example of reaction **0-97** (p. 370). In the last step the enol lactone (butenolide) formed by the 1,3-dipolar addition is hydrolyzed by base. It may be noted that the 1,3-dipolar species **57** does not fit into either of the two main categories mentioned above. Although **57** adds to the double bond of ketene, it normally undergoes rearrangement (reaction **8-8,** p. 809) before it can add to most other double bonds.[254]

OS **46,** 96, 127. Also see OS **IV,** 380.

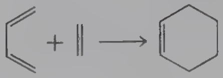
C. Carbon on one or both sides. Reactions **5-34** to **5-37** are cycloadditions in which carbon is added to both sides of the double bond.

---

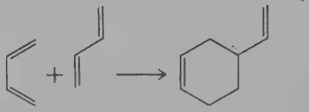
[253] Ried and Mengler, *Ann.* **678,** 113 (1964).

[254] Huisgen, Binsch, and Ghosez, *Chem. Ber.* **97,** 2628 (1964).

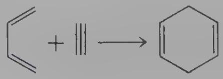
5-34 The Diels-Alder reaction



In the *Diels-Alder reaction* a double bond adds 1,4 to a conjugated diene (a 4 + 2 cycloaddition)[255] so that the product is always a six-membered ring. The double-bond compound is called a *dienophile*. The reaction is very easy and rapid, and of very broad scope. Ethylene and simple olefins make poor dienophiles, although the reaction has been carried out with these compounds. Most dienophiles are of the form $—\underset{|}{C}=\underset{|}{C}—Z$ or $Z—\underset{|}{C}=\underset{|}{C}—Z'$, where Z and Z′ are CHO, COR, COOH, COOR, COCl, COAr, CN,[256] NO_2,[257] Ar, CH_2OH, CH_2Cl, CH_2NH_2, CH_2CN, CH_2COOH, halogen, or C=C.[258] In the latter case, the dienophile is itself a diene:



When two dienes react, then mixtures are quite possible. Thus, butadiene and isoprene ($CH_2=CH—CMe=CH_2$) gave all nine possible Diels-Alder adducts, as well as eight-membered rings and trimers.[259] Particularly common dienophiles are maleic anhydride[260] and quinones.[261] Triple bonds ($—C{\equiv}C—Z$ or $Z—C{\equiv}C—Z'$) may be dienophiles



---

[255] For a monograph, see Wasserman, "Diels-Alder Reactions," Elsevier Publishing Co., New York, 1965. For reviews, see Huisgen, Grashey, and Sauer, Ref. 252, pp. 878–929; Alder, in "Newer Methods in Preparative Organic Chemistry," vol. 1, pp. 381–511, Interscience Publishers, Inc., New York, 1948; and Sauer, *Angew. Chem. Intern. Ed. Engl.* **5,** 211–230 (1966), **6,** 16–33 (1967).

[256] For a review of the Diels-Alder reaction with acrylonitrile, see Butskus, *Russ. Chem. Rev.* **31,** 283–284 (1962).

[257] For a review of the Diels-Alder reaction with nitro compounds, see Novikov, Shuekhgeimer, and Dudinskaya, *Russ. Chem. Rev.* **29,** 79–94 (1960).

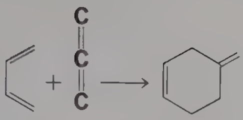
[258] For a review of Diels-Alder reactions with many ethylenic and acetylenic dienophiles, see Holmes, *Org. Reactions* **4,** 60–173 (1948).

[259] Johnstone and Quan, *J. Chem. Soc.* **1963,** 935.

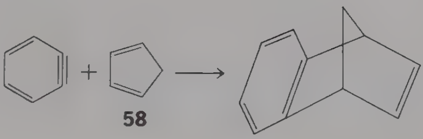
[260] For a review of Diels-Alder reactions with maleic anhydride, see Kloetzel, *Org. Reactions* **4,** 1–59 (1948).

[261] For a review of Diels-Alder reactions with quinones, see Butz and Rytina, *Org. Reactions* **5,** 136–192 (1949).

as may allenes

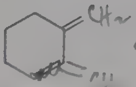


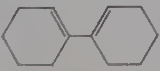
Benzynes, although not isolable, act as dienophiles, and may be trapped with dienes;[262] for example,

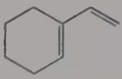

58

Besides carbon-carbon multiple bonds, other double- and triple-bond compounds may be dienophiles, giving rise to heterocyclic compounds. Among these are N≡C—, —N=C—, —N=N—, O=N, and —C=O compounds[263] and, as we have seen (reaction **5-30**), even molecular oxygen.

Dienes may be open-chain, inner-ring (e.g., **58**), outer-ring (e.g., **59**), across rings (e.g., **60**), or inner-outer (e.g., **61**), except that they may not be frozen into a transoid conformation (see p. 629). They need no special activating groups, and nearly all conjugated dienes undergo the reaction with suitable dienophiles.[264]


59


60


61

Aromatic compounds may also behave as dienes. Benzene is very unreactive toward dienophiles, and only benzyne has been reported to give a Diels-Alder adduct with it.[265] Naphthalene and phenanthrene are also quite resistant, though naphthalene has given Diels-Alder addition at high pressures.[266]

---

[262] Wittig and Pohmer, *Chem. Ber.* **89,** 1334 (1956); Wittig and Knauss, *Chem. Ber.* **91,** 895 (1958); Wittig and Dürr, *Ann.* **672,** 55 (1964).

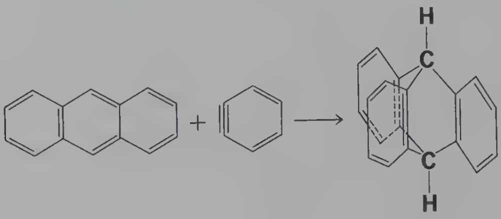
[263] For a review of dienes and dienophiles with hetero atoms, see Needleman and Chang Kuo, *Chem. Rev.* **62,** 405–431 (1962). For a review of dienophiles with hetero atoms, see Arbuzov, *Russ. Chem. Rev.* **33,** 407–424 (1964).

[264] For a review of Diels-Alder reactions with cyclopentadienone as diene, see Allen, *Chem. Rev.* **62,** 653–664 (1962). For a review with perchlorocyclopentadiene, see Ungnade and McBee, *Chem. Rev.* **58,** 249–320 (1958), pp. 254–305.

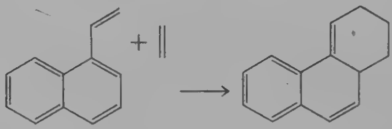
[265] Miller and Stiles, *J. Am. Chem. Soc.* **85,** 1798 (1963); Meyerson and Fields, *Chem. Ind. (London)* **1966,** 1230.

[266] Jones, Mangold, and Plieninger, *Tetrahedron* **18,** 267 (1962).

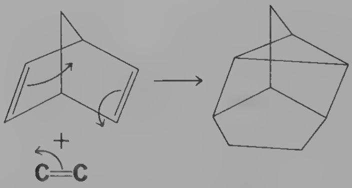
However, anthracene and other compounds with at least three linear benzene rings give Diels-Alder reactions readily. The interesting compound triptycene can be prepared by a Diels-Alder reaction between benzyne and anthracene:[267]



It is possible for a diene to have one double bond in an aromatic system, and the other outside it, e.g.,



Even styrene has been shown to react in this manner.[268] Certain heterocyclic aromatic rings may also behave as dienes in the Diels-Alder reaction. Among these is furan, but not thiophene or pyrrole (another indication that furan is less aromatic than the other two, see p. 40). Some hetero dienes which give the reaction are —C=C—C=O, O=C—C=O, and N=C—C=N.[255] For both all-carbon and hetero systems, the "diene" may be a conjugated enyne or even a diyne. If the geometry of the molecule is suitable, the diene may even be nonconjugated, e.g.,[269]



The stereochemistry of the Diels-Alder reaction may be considered from several aspects:[270]

---

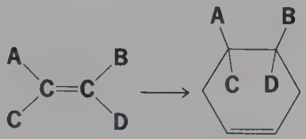
[267] Wittig and Niethammer, *Chem. Ber.* **93**, 944 (1960); Wittig, Härle, Knauss, and Niethammer, *Chem. Ber.* **93**, 951 (1960).

[268] Lora-Tamayo, *Tetrahedron* **4**, 17 (1958).

[269] Cookson, Dance, and Hudec, *J. Chem. Soc.* **1964**, 5416.

[270] For a review, see Martin and Hill, *Chem. Rev.* **61**, 537–562 (1961).

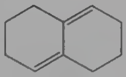
1. With respect to the dienophile, the addition is always cis. No exceptions are known. This means that groups which are cis in the olefin will be cis in the cyclohexene ring:



The addition is thus stereospecific.

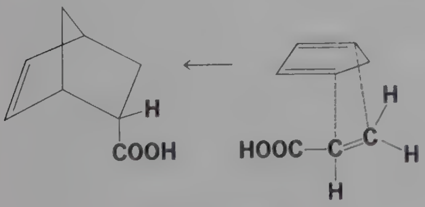
2. For 1,4-disubstituted dienes, the reaction also seems to be stereospecific and cis, although fewer cases have been investigated than for dienophiles. Thus, *trans,trans*-1,4-diphenylbutadiene gives *cis*-1,4-diphenylcyclohexene derivatives.

3. The diene must be in the cisoid conformation. If it is frozen into the transoid conformation, as in **62**, the reaction does not take place. For example, 7,9-cholestadiene has such a transoid system and is inert to maleic anhydride. The diene, therefore must be either frozen into the cisoid conformation or must be able to achieve it during the reaction.

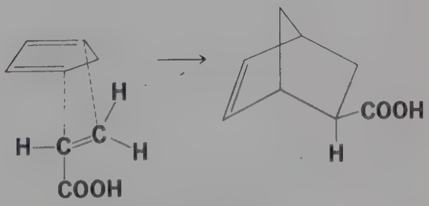


62

4. When the diene is cyclic, there are two possible ways in which addition can occur, if the dienophile is not symmetrical. The larger side of the dienophile may be under the ring (*endo addition*), or it may be the smaller side (*exo addition*):



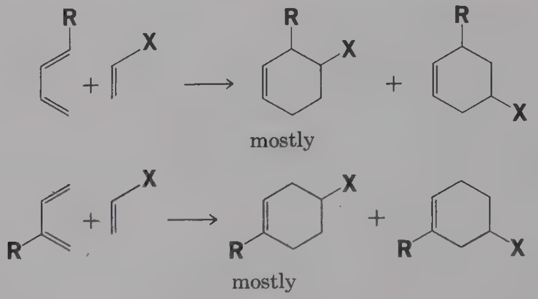
Endo addition



Exo addition

Most of the time, the addition is predominantly endo; that is, the more bulky side of the olefin is under the ring, and this is probably true for open-chain dienes also. However, exceptions are known, and in many cases mixtures of exo and endo addition products are found.[271]

When an unsymmetrical diene adds to an unsymmetrical dienophile, there are two possible products (not counting stereoisomers):



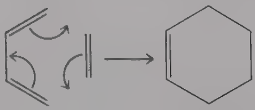
Although mixtures are often obtained, usually one predominates,[272] the one indicated above.

Electron-donating substituents in the diene accelerate the reaction; electron-withdrawing groups retard it. For the dienophile it is just the reverse: donating groups decrease the rate, and withdrawing groups increase it. Cyclic dienes, in which the cisoid conformation is built in, usually react faster than the corresponding open-chain compounds, which have to achieve the cisoid conformation by rotation.[273]

As should be apparent from the foregoing, many interesting compounds may be prepared by the Diels-Alder reaction, some of which we would be hard put to make in any other way. It has thus been exceedingly useful. Competing reactions are polymerization of the diene or dienophile, or both, and 1,2 cycloaddition (reaction **5-35**). However, yields are usually quite high. No catalyst is needed, although it has been found that Lewis acids catalyze some Diels-Alder reactions.[274] The Diels-Alder reaction is usually reversible and has been used to "protect" double bonds.

The mechanism of the reaction is still not fully settled. There are, broadly speaking, two possible mechanisms which have been advanced. In mechanism *a* there is a cyclic six-centered transition state and no intermediate. The reaction is concerted and occurs in one step:

Mechanism *a*:



---

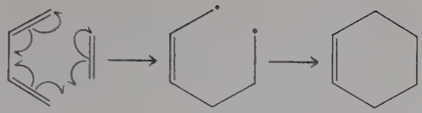
[271] See, for example, Alder and Günzl, *Chem. Ber.* **93**, 809 (1960); Stockmann, *J. Org. Chem.* **26**, 2025 (1961).

[272] For a review, see Titov, *Russ. Chem. Rev.* **31**, 267–282 (1962).

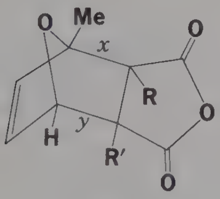
[273] Sauer, Lang, and Mielert, *Angew. Chem. Intern. Ed. Engl.* **1**, 268 (1962); Sauer and Wiest, *Angew. Chem. Intern. Ed. Engl.* **1**, 269 (1962).

[274] Yates and Eaton, *J. Am. Chem. Soc.* **82**, 4436 (1960); Fray and Robinson, *J. Am. Chem. Soc.* **83**, 249 (1961).

Mechanism *b*:



In mechanism *b* one end of the diene fastens to one end of the dienophile first, and then the other ends become fastened. Proponents of mechanism *b* usually do not state whether this initial bond (and, of course, the subsequent bond) is formed by a free-radical process (as we have depicted it), in which case the intermediate is a diradical, or in an ionic process, in which case the intermediate is a diion. If it is a diradical, then it must be a singlet; that is, the two unpaired electrons must have opposite spins,[275] by an argument similar to that outlined on page 160. In either case such an ion or radical would be stabilized by resonance with the newly formed double bond. It may be that mechanisms *a* and *b* represent extremes, like S_N1 and S_N2 (which also differ only in the timing of the steps), and that they operate in different cases. Most evidence is compatible with both types of mechanism. However, there is one important result which is compatible only with mechanism *a*. It was shown that, in the decomposition of **63**, the isotope effect k_I/k_{II} was equal to 1.00 within experimental error.[276] If bond *x* broke before bond *y*, then there should surely be a secondary isotope effect. This result strongly indicates that the bond breaking of *x* and *y* is simultaneous. This is the reverse of a Diels-Alder reaction, and by the principle of microscopic reversibility, the mechanism of the forward reaction should involve simultaneous formation of bonds *x* and *y*. Subsequently, a similar experiment was carried out on the forward reaction,[277] and the result was the same. The stereospecificity also seems to favor mechanism *a*, but Woodward and Katz have argued that this is also compatible with mechanism *b*.[278] According to them the first bond is formed by the two compounds lying above each other in parallel planes, and then "conformational specificity about the newly formed bond is determined by secondary attractive forces involving electrons not directly associated with the primary bonding process." Kinetic and thermodynamic evidence also favors mechanism *a* since the data show that there is a rigid activated complex, but the proposal of Woodward and Katz



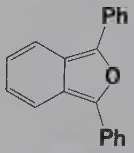
63

I: R = H, R′ = D
II: R = D, R′ = H

---

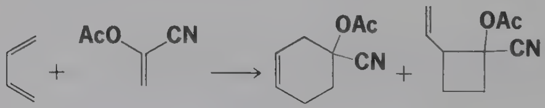
[275] Walling and Schugar, *J. Am. Chem. Soc.* **85**, 607 (1963).
[276] Seltzer, *J. Am. Chem. Soc.* **85**, 1360 (1963), **87**, 1534 (1965).
[277] Van Sickle and Rodin, *J. Am. Chem. Soc.* **86**, 3091 (1964).
[278] Woodward and Katz, *Tetrahedron* **5**, 70 (1959).

shows that a rigid complex is also compatible with mechanism *b*. Some of the evidence in favor of mechanism *b* is as follows: **64** forms adducts easily with cyclic dienophiles, but, if the two phenyl groups are replaced by mesityl groups, no Diels-Alder reaction takes place.[279] This is easily explained by a



64

steric hindrance which prevents the dienophile from lying in the proper position. If only one phenyl is replaced by a mesityl, the dienophile still cannot lie in the proper position, *but the reaction with vinylene carbonate does take place.* This may be explained by the hypothesis that steric hindrance does not prevent the bond from forming on one side and that, once this occurs, the intermediate finds it easier to form the adduct than to reverse the first step. Other evidence is drawn from spectral studies. In some cases transient colors are formed, which can possibly be attributed to the intermediate. It has been shown spectroscopically that maleic anhydride and thiophene, which do not form an adduct, nevertheless form a 1:1 complex,[280] and that a similar complex is formed from maleic anhydride and furan, which do form an adduct. It may be that this complex, or some species closely related to it, is the intermediate. Additional evidence for the intervention of an intermediate was obtained by Little, who showed that in the reaction between butadiene and 1-cyanovinyl acetate, both the normal Diels-Alder adduct and the four-membered cyclization product (reaction **5-35**) were produced:[281]



The obtention of both types of product is not uncommon, but what was significant was the fact that the ratio of the two products (about 4:1) was very little dependent on solvent or temperature, indicating that both products are probably formed through a common transition state. If there is a common transition state, then one bond must be formed before the other, since, for example, a transition state in which considerable progress had been made toward formation of both bonds could not result in both products. Certain substituent effects and evidence from activation volumes[275] are also in favor of the two-step process.

Turning to another aspect of the mechanism, the effects of electron-donating and -withdrawing substituents (p. 573) indicate that the diene is behaving as a nucleophile and the dienophile as an electrophile. However, this can be reversed. Perchlorocyclopentadiene reacts better with cyclopentene than with maleic anhydride, and not at all with tetracyanoethylene, though the latter is normally the most reactive dienophile known. It is apparent, then, that this diene is the electrophile in its Diels-Alder reactions.[282]

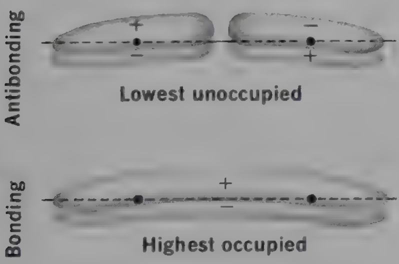
---

[279] Newman, *J. Org. Chem.* **26**, 2630 (1961).

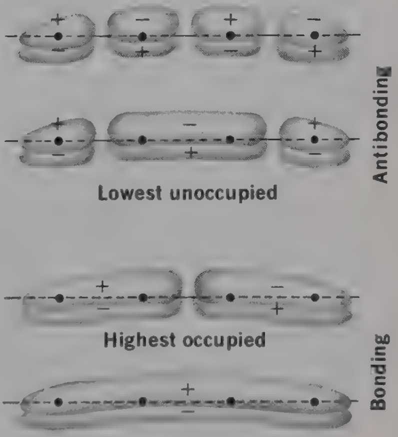
[280] Arbuzov and Konovalov, *Bull. Acad. Sci. USSR* **1959**, 2032, **1960**, 59.

[281] Little, *J. Am. Chem. Soc.* **87**, 4020 (1965). See also Banks, Harrison, and Haszeldine, *Chem. Commun.* **1966**, 338.

We have emphasized that the Diels-Alder reaction generally takes place rapidly and conveniently. In sharp contrast, the apparently similar dimerization of olefins to cyclobutanes (reaction **5-35**) gives very poor results in most cases. This difference in reactivity may be explained by the principle of *conservation of orbital symmetry*.[283] As applied to these reactions, the rule is that *reactions are allowed only when all overlaps between the highest-occupied molecular orbital of one reactant and the lowest-unoccupied molecular orbital of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe.* We may recall that monoolefins have two π molecular orbitals (p. 13) and that conjugated dienes have four (p. 31), as shown in the following schematic drawings:

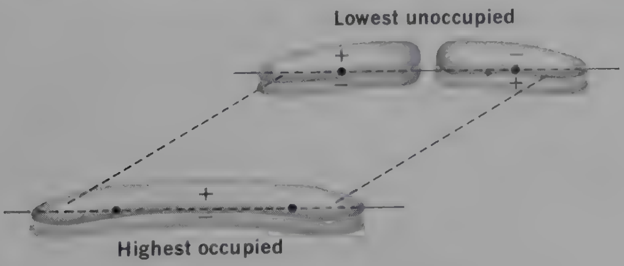


π orbitals of an isolated C$=$C bond.



π orbitals of a conjugated diene

A concerted cyclization of two monoolefins (a 2 + 2 reaction) is not allowed, because it would require that a positive lobe overlap with a negative lobe:

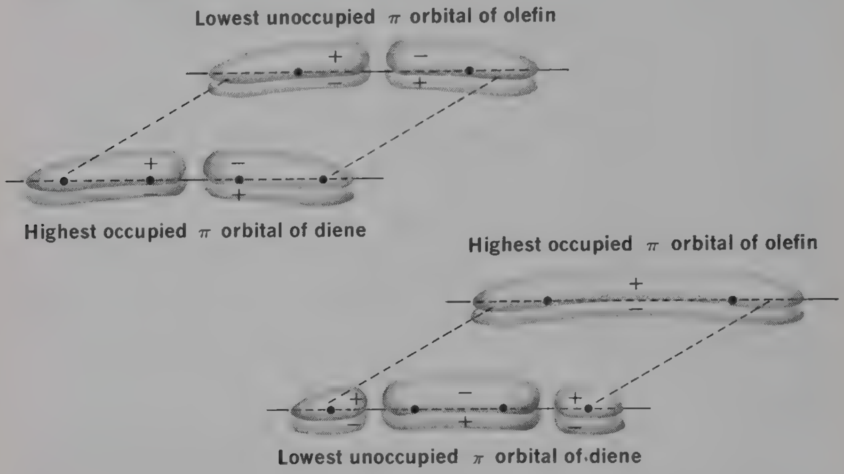


---

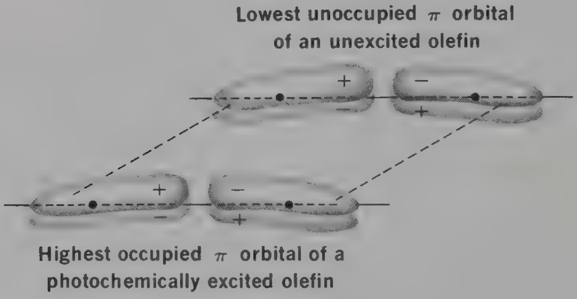
[282] Sauer and Wiest, *Angew. Chem. Intern. Ed. Engl.* **1**, 269 (1962).

[283] Hoffmann and Woodward, *J. Am. Chem. Soc.* **87**, 2046, 4388 (1965).

On the other hand, the Diels-Alder reaction (a 4 + 2 reaction) is allowed, whether considered from either direction:


Lowest unoccupied π orbital of olefin
Highest occupied π orbital of diene
Highest occupied π orbital of olefin
Lowest unoccupied π orbital of diene

These considerations are reversed when the ring closures are photochemically induced, since in such cases an electron is promoted to a vacant orbital before the reaction occurs. Obviously, the 2 + 2 reaction is now allowed:


Lowest unoccupied π orbital
of an unexcited olefin
Highest occupied π orbital of a
photochemically excited olefin

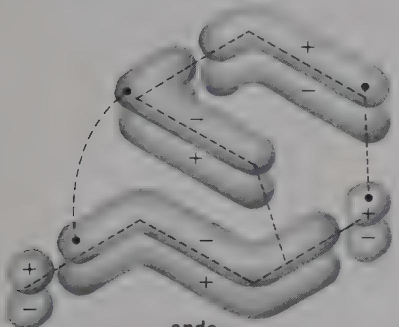
and the 4 + 2 reaction disallowed.

The reverse reactions follow the same rules, by the principle of microscopic reversibility. In fact, Diels-Alder adducts are usually cleaved quite readily, while cyclobutanes, despite the additional strain, require more strenuous conditions. We therefore predict that 2 + 2, 4 + 4, and 6 + 2 ring closures (and the reverse ring openings) will occur by cyclic mechanisms only when photochemically induced, while 4 + 2, 6 + 4, and 8 + 2 ring closures (and openings) will occur only thermally.

It must be emphasized, however, that the rule applies only to reactions which take place by cyclic mechanisms, that is, where two σ bonds are formed (or broken) at about the same time. The rule does not apply to cases where one bond is clearly formed (or broken) before the other.

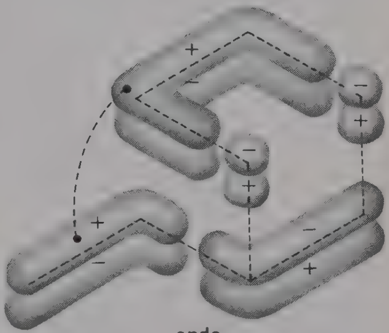
Indeed, we shall see (in reaction **5-35**) that 2 + 2 ring closures largely do occur by two-step mechanisms.

Symmetry considerations have also been advanced to explain predominant endo addition.[284] In the case of 4 + 2 addition of butadiene to itself, the approach may be exo or endo:



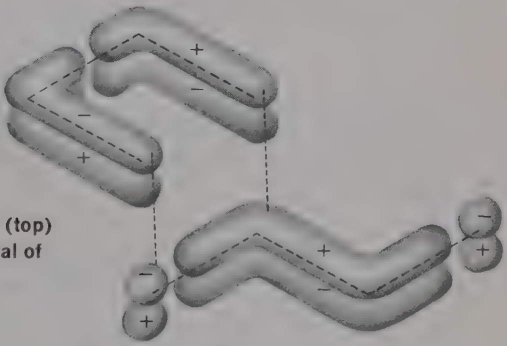
endo

Highest-occupied orbital of diene (top) overlaps lowest-unoccupied orbital of "olefin" (bottom)



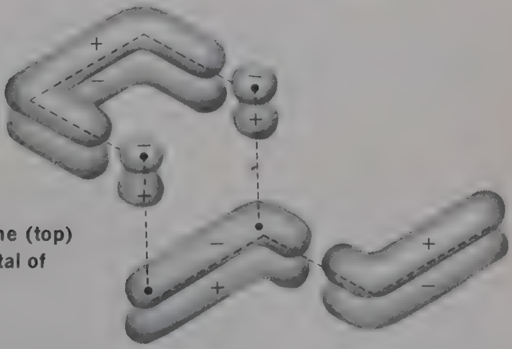
endo

Lowest-unoccupied orbital of diene (top) overlaps highest occupied orbital of "olefin" (bottom)



exo

Highest-occupied orbital of diene (top) overlaps lowest-unoccupied orbital of "olefin" (bottom)



exo

Lowest unoccupied orbital of diene (top) overlaps highest-occupied orbital of "olefin" (bottom)

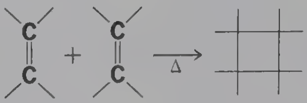
---

[284] Hoffmann and Woodward, *J. Am. Chem. Soc.* **87**, 4388 (1965). For another view, see Herndon and Hall, *Tetrahedron Letters* **1967**, 3095.

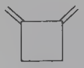
It may be seen that whether the highest-occupied molecular orbital of the diene overlaps with the lowest-unoccupied molecular orbital of the olefin or vice versa, the endo orientation is stabilized by additional secondary overlap of orbitals of like sign (dashed lines between heavy dots). Addition from the exo direction has no such stabilization.

OS **II,** 102; **III,** 310, 807; **IV,** 238, 311, 738, 890, 964; **40,** 85; **42,** 50. Also see OS **46,** 44, 107.

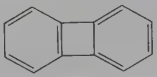
5-35 Dimerization of olefins



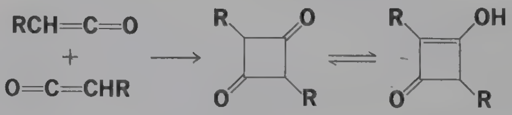
The reaction between two molecules of olefin to give cyclobutane derivatives (a 2 + 2 cycloaddition) may be carried out where the olefins are the same or different, but the reaction is not a general one for olefins.[285] Dimerization of like olefins occurs with the following compounds: $F_2C{=}CX_2$ ($X = F$ or Cl) and certain other fluorinated alkenes, though not $F_2C{=}CH_2$, allenes (to give derivatives of **65**),[286] benzynes [to give biphenylene (**66**) derivatives], and activated olefins (e.g., styrene, acrylonitrile, butadiene, etc.). Ketenes dimerize to give cyclobutenone derivatives (**67**) as the major primary products:



65

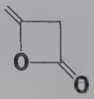


66



67

except that ketene itself dimerizes in a different manner, with a C=C bond adding to a C=O bond to give the unsaturated β-lactone **68** (reaction **6-65,** p. 723).[287]



68

---

[285] For reviews, see Roberts and Sharts, *Org. Reactions* **12,** 1-56 (1962); Wilson and Goldhamer, *J. Chem. Educ.* **40,** 599-603 (1963); and Huisgen, Grashey, and Sauer, Ref. 252, pp. 779-802.

[286] For a review, see Fischer, in Patai, "The Chemistry of Alkenes," pp. 1064-1067, Interscience Publishers, Inc., New York, 1964.

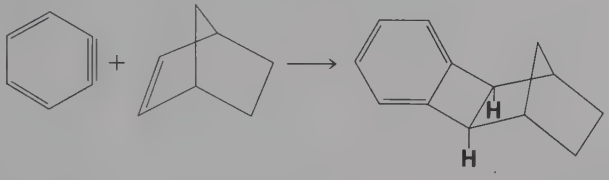
[287] Farnum, Johnson, Hess, Marshall, and Webster, *J. Am. Chem. Soc.* **87,** 5191 (1965). For a review, see Hanford and Sauer, *Org. Reactions* **3,** 127-132 (1946).

Different olefins combine as follows:

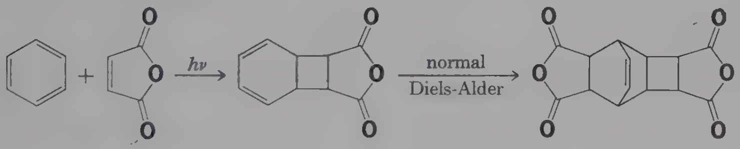
1. $F_2C{=}CX_2$ (X = F or Cl), especially $F_2C{=}CF_2$, form cyclobutanes with many olefins. Compounds of this type even react with conjugated dienes to give four-membered rings rather than undergoing normal Diels-Alder reactions.[288]

2. Allenes and ketenes react with activated olefins and alkynes. Ketenes give 1,2 addition even with conjugated dienes.[289]

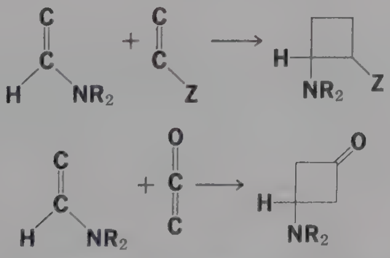
3. Benzynes react with certain olefins,[290] e.g.,



4. Maleic anhydride and maleimide react with benzene and phenanthrene, under the influence of ultraviolet light (shown for maleic anhydride; maleimide reacts analogously):[291]



5. Enamines form four-membered rings with Michael-type olefins[292] and with ketenes.[293] In both cases, only enamines from aldehydes give stable four-membered rings:



---

[288] Bartlett, Montgomery, and Seidel, *J. Am. Chem. Soc.* **86,** 616 (1964).

[289] See, for example, Martin, Gott, Goodlett, and Hasek, *J. Org. Chem.* **30,** 4175 (1965).

[290] Simmons, *J. Am. Chem. Soc.* **83,** 1657 (1961).

[291] Angus and Bryce-Smith, *J. Chem. Soc.* **1960,** 4791; Grovenstein, Rao, and Taylor, *J. Am. Chem. Soc.* **83,** 1705 (1961); Bryce-Smith and Vickery, *Chem. Ind.* (*London*) **1961,** 429; Bryce-Smith, Gilbert, and Vickery, *Chem. Ind.* (*London*) **1962,** 2060; Bryce-Smith and Gilbert, *J. Chem. Soc.* **1965,** 918; Bryce-Smith and Hems, *Tetrahedron Letters* **1966,** 1895; Bradshaw, *Tetrahedron Letters* **1966,** 2039.

[292] Brannock, Bell, Burpitt, and Kelly, *J. Org. Chem.* **29,** 801 (1964); Brannock, Bell, Goodlett, and Thweatt, *J. Org. Chem.* **29,** 813 (1964). For a review of enamine reactions, see Szmuszkovicz, *Advan. Org. Chem.* **4,** 1–113 (1963), pp. 39–42.

[293] Berchtold, Harvey, and Wilson, *J. Org. Chem.* **26,** 4776 (1961); Hasek and Martin, *J. Org. Chem.* **28,** 1468 (1963); Opitz and Kleeman, *Ann.* **665,** 114 (1963); Hasek, Gott, and Martin, *J. Org. Chem.* **31,** 1931 (1966).

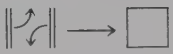
The reaction of enamines with ketenes may be conveniently carried out by generating the ketene *in situ* from an acyl halide and a tertiary amine. It has been possible to isolate *cyclobutenes* by treatment of C≡C—Z with enamines,[294] but these more often rearrange.[295]

6. Olefins with electron-withdrawing groups may form cyclobutanes with olefins containing electron-donating groups. The enamine reactions, mentioned above, are examples of this, but it has also been accomplished for olefins containing OR and SR groups (enol and thioenol ethers).[296]

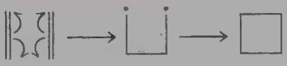
Solvents are not necessary for 2 + 2 cycloadditions. They are usually carried out at 100 to 225° under pressure, though the reactions in group 6 occur under milder conditions.

The reaction is similar to the Diels-Alder (in action, not in scope), and if dienes are involved, the latter reaction may compete, though most olefins react with a diene either entirely by 1,2 or entirely by 1,4 addition. Two mechanisms have been proposed, analogous to those proposed for the Diels-Alder reaction:

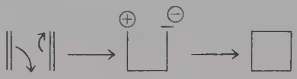
Mechanism *a*:



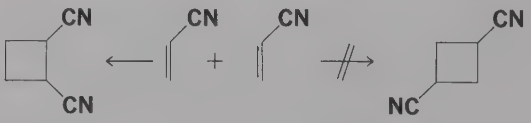
Mechanism *b*:



It is also possible to picture mechanism *b* as involving a diionic intermediate rather than a diradical:



For most of the dimerizations, a diionic intermediate is extremely unlikely, because unsymmetrical olefins usually give head-to-head coupling, rather than head-to-tail; for example, dimerization of acrylonitrile gives **69** and not **70**. If one pair of electrons moved before the other, then the positive end



69 **70**

of one molecule would be expected to attack the negative end of the other. Another fact arguing against a diion is that the reactions proceed well in nonpolar solvents and in the gas phase. However, some reactions, notably those in groups 5 and 6, probably do react by a diion mechanism, and head-to-tail coupling is found there.

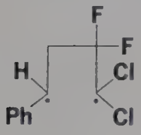
---

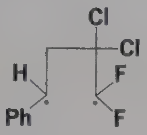
[294] Huebner, Dorfman, Robison, Donoghue, Pierson, and Strachan, *J. Org. Chem.* **28**, 3134 (1963).

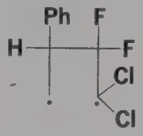
[295] Brannock, Burpitt, Goodlett, and Thweatt, *J. Org. Chem.* **29**, 818 (1964).

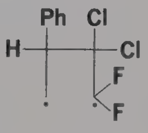
[296] Williams, Wiley, and McKusick, *J. Am. Chem. Soc.* **84**, 2210 (1962).

The principle of conservation of orbital symmetry (p. 633) rules out mechanism *a* (except for photochemical reactions), and indeed, for the majority of reactions, the evidence is in favor of mechanism *b* with a diradical intermediate. As in reaction **5-34**, the diradical must be a singlet. Among the evidence for the diradical mechanism is the fact that, when unsymmetrical olefins couple, the orientation of the product can almost always be predicted on the basis of the relative stability of the radicals; for example, styrene and $F_2C{=}CCl_2$ can give four intermediates:

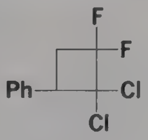

71


72

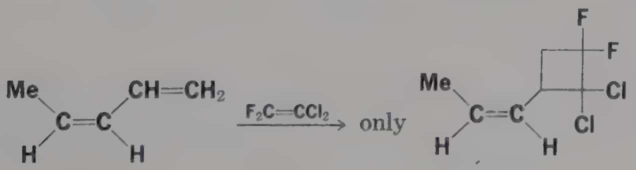

73

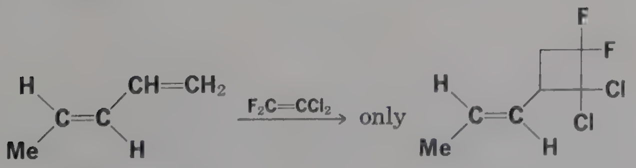

74

On the basis of radical stability, **73** and **74** may be ruled out, since in **71** and **72** there is resonance of an unpaired electron with a phenyl group. **71** is more likely than **72**, since a dichloromethyl type of radical should be more stable than a difluoromethyl type. In accord with this prediction, the product is actually **75**.[297] Similarly, for a diene, it is possible to predict


75

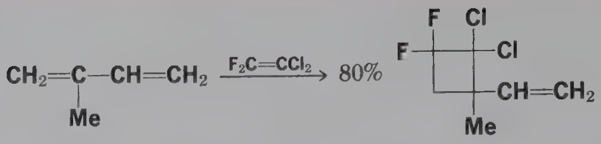
which double bond will be attacked on the basis of which radical is most stable. In the reaction between $F_2C{=}CCl_2$ and *cis*- (**76**) and *trans*-1,3-pentadiene (**77**) and isoprene, the products were those predicted in this manner:[288]


76

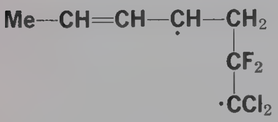

77

---

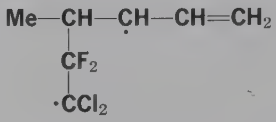
[297] Silversmith, Kitahara, Caserio, and Roberts, *J. Am. Chem. Soc.* **80**, 5840 (1958).



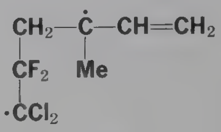
If the mechanism is a diradical one, then attack will always be at the end of the conjugated system (p. 577). For **76** or **77**, an attack at C-1 gives a radical (**78**) stabilized by hyperconjugation with the methyl, while attack at C-4 gives a radical (**79**) not thus stabilized. Likewise, for isoprene, both possible radicals (**80** and **81**) are stabilized by resonance with the double bond, but only **80** is further stabilized by the methyl group. Not only are the products in accord with these predictions, but, as in the previous instance, it is the CF_2 group which makes the initial attack. Further evidence for mechanism *b* is that these reactions are not stereoselective.[298]



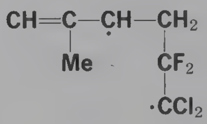
78



79



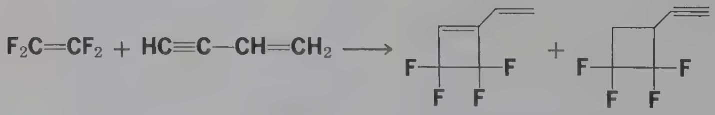
80



81

In this reaction, as in reaction **5-34**, one molecule may be regarded as a nucleophile and the other as an electrophile, at least in some cases. For example, tetrafluoroethylene and butadiene react with each other faster than either does with itself.

In some cases, double bonds add to triple bonds to give cyclobutenes, apparently at about the same rate that they add to double bonds; for example,



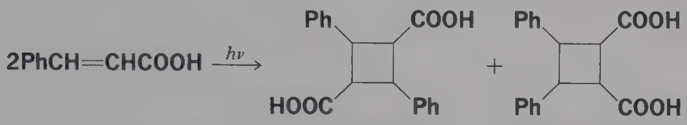
About equal amounts

The addition of triple bonds to triple bonds would give cyclobutadienes, and this has not been observed, except in instances where these rearrange before they can be isolated (see reaction **5-36**).

---

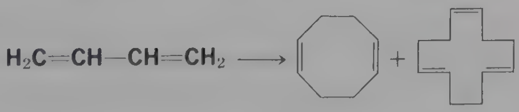
[298] Montgomery, Schueller, and Bartlett, *J. Am. Chem. Soc.* **86,** 621 (1964).

Many olefins dimerize, even if not in the above classes, under ultraviolet light;[299] for example,

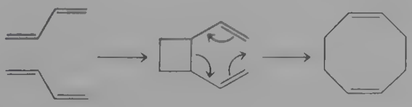

Truxillic acids   Truxinic acids

This is just what we would expect from the principle of conservation of orbital symmetry (p. 633). Photochemical dimerization also occurs in the solid state. Since the molecules here have no freedom of motion, the only reactions which can occur are those where only a minimum of atomic or molecular motion is required. Only the electrons can move much. The dimerization of olefins is well suited to these limitations. In the solid state, closely related compounds may react quite differently. For example, $PhCH{=}CH{-}CH{=}C(COOH)_2$ gives a dimer where the two molecules are connected at the γ and δ positions, while $PhCH{=}CH{-}CH{=}CHCOOH$ gives a dimer where one molecule is connected by its α and β positions and the other by its γ and δ positions.[300] This result is found because the molecules are stacked differently in the lattice, and the principle of minimum motion is followed. A given compound may react one way in the solid phase and another way in freer phases. For example, the dimerization of cinnamic acid, pictured above, occurs *only* in the solid state. Also, different crystalline modifications of a compound may react differently, since the stacking is not the same. Cinnamic acid supplies an example here too, since it is different crystalline forms which give rise to the truxillic acids (a mixture of stereoisomers) on the one hand, and the truxinic acids on the other. The study of reactions in the solid state is called *topochemistry*.[301]

Conjugated dienes may be dimerized and even trimerized at their 1,4-positions, under the right conditions. Thus, butadiene under heat and pressure gives 1,5-cyclooctadiene and 1,5,9-cyclododecatriene:



These compounds probably arise, not by direct 1,4-to-1,4 attack, but by the initial closing of a four- or six-membered ring, followed by a Cope rearrangement (reaction **8-26**, p. 834), for example,



OS **42**, 44; **43**, 17, 27; **46**, 34.

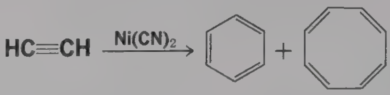
---

[299] For a review, see Mustafa, *Chem. Rev.* **51**, 1–23 (1951).

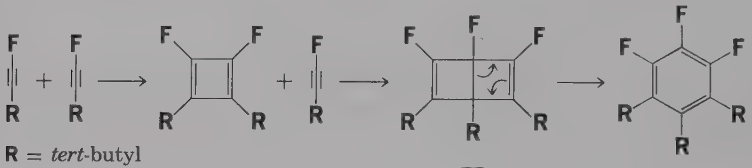
[300] Cohen and Schmidt, *J. Chem. Soc.* **1964**, 1996.

[301] Cohen, Hirschberg, and Schmidt, *J. Chem. Soc.* **1964**, 2060, and seven preceding papers.

5-36 Trimerization and tetramerization of alkynes



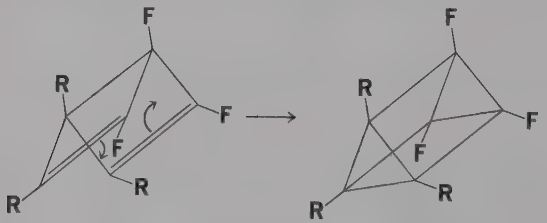
When acetylene is heated with nickel cyanide, other Ni(II) or Ni(0) compounds, or similar catalysts, it gives benzene and cyclooctatetraene.[302] It is possible to get more of either product by a proper choice of catalyst. Substituted acetylenes give substituted benzenes.[303] This reaction has been used to prepare very crowded molecules. Diisopropylacetylene was trimerized over $Co_2(CO)_8$ and over $Hg[Co(CO)_4]_2$ to hexaisopropylbenzene, which had previously been unknown.[304] The six isopropyl groups are not free to rotate but are lined up perpendicular to the plane of the benzene ring. Even more interesting was the *spontaneous* (no catalyst) trimerization of *tert*-BuC≡CF to give 1,2,3-tri-*tert*-butyl-4,5,6-trifluorobenzene (**83**), the first time three adjacent *tert*-butyl groups had been put onto a benzene ring.[305] The fact that this is a head-to-head joining makes the following sequence likely:



R = *tert*-butyl

82 **83**

The fact that **82** (a bicyclo[2.2.0]hexadiene) was also isolated lends support to this scheme. Also isolated was **84**, a derivative of prismane, and the first derivative of this compound to be prepared. The formation of **84** is further evidence for the scheme shown above, since it could be formed as follows:



82 **84**

---

[302] For a review, see Schrauzer, Glockner, and Eichler, *Angew. Chem. Intern. Ed. Engl.* **3,** 185–191 (1964).

[303] See, for example, Franzus, Canterino. and Wickliffe, *J. Am. Chem. Soc.* **81,** 1514 (1959); Reikhsfel'd, Makovetskii, and Erokhina, *J. Gen. Chem. USSR* **32,** 646 (1962).

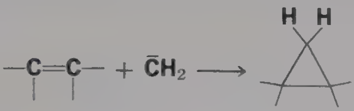
[304] Arnett and Bollinger, *J. Am. Chem. Soc.* **86,** 4729 (1964); Hopff, *Chimia* **18,** 140 (1964); Hopff and Gati, *Helv. Chim. Acta* **48,** 509 (1965).

[305] Viehe, Merényi, Oth, and Valange, *Angew. Chem. Intern. Ed. Engl.* **3,** 746 (1964); Viehe, Merényi, Oth, Senders, and Valange, *Angew. Chem. Intern. Ed. Engl.* **3,** 755 (1964). Also see Arnett and Bollinger, *Tetrahedron Letters* **1964,** 3803.

Bicyclo[2.2.0]hexadienes and prismanes are *valence isomers* of benzenes.[306] These compounds actually have the structures which in the nineteenth century were proposed for benzenes. Prismanes have the Ladenburg formula, and bicyclo[2.2.0]hexadienes have the Dewar formula. On page 28 it was mentioned that Dewar formulas are canonical forms (though not very important) of benzenes. Yet they may also exist as separate compounds in which the positions of the nuclei are different from those of benzenes. That is, if one were to move the six ring carbon atoms of **82** to the positions of a normal benzene ring, the electrons would reorient themselves into the familiar aromatic sextet. Indeed, this is just what happens when **82** is converted to **83.**

For addition of triple bonds to triple bonds, but not with ring formation, see reaction **5-14.**

5-37 The addition of carbenes and carbenoids to double and triple bonds



Carbenes and substituted carbenes add to double bonds to give cyclopropane derivatives (2 + 1 cycloaddition).[307] Although many derivatives of carbene have been added to double bonds, the reaction is most often performed with CH_2 itself, and with dihalo carbenes.[308] Alkylcarbenes, HCR, have been added to olefins,[309] but more often these rearrange to give olefins (p. 165). The carbene may be generated in any of the ways normally used (p. 162). However, not all reactions in which a cyclopropane is formed by treatment of an olefin with a carbene "precursor" actually involve free carbene intermediates. In some cases (e.g., the Simmons-Smith procedure, p. 648) it is certain that free carbenes are not involved, and in other cases there is doubt. The term *carbenoid* is used where carbene-like addition is found, but free carbene intermediates are not involved.

Carbene itself is extremely reactive and gives many side reactions, especially insertion reactions (**2-11**, p. 466), which greatly reduce yields.[310] When it is desired to add CH_2 for preparative purposes, free carbene is not used, but the Simmons-Smith procedure, or some other method which does not involve free carbenes, is employed instead. Halocarbenes are less active than carbenes, and this reaction proceeds quite well, since insertion reactions do not interfere. The order of reactivity is $CH_2 > CHCl > CCl_2 > CBr_2 > CF_2$. Among the many ways in which dihalocarbenes or carbenoids are generated for this reaction are the following, all of which involve α-elimination (the first two steps of the S_N1cB mechanism, p. 293):

---

[306] For reviews of valence isomers of benzene, see van Tamelen, *Angew. Chem. Intern. Ed. Engl.* **4,** 738–745 (1965); and Viehe, *Angew. Chem. Intern. Ed. Engl.* **4,** 746–751 (1965).

[307] For reviews, see Patai, "The Chemistry of Alkenes," Interscience Publishers, Inc., New York, 1964, as follows: Cadogan and Perkins, pp. 633–671; Huisgen, Grashey, and Sauer, pp. 755–776. Other reviews are by Kirmse, *Angew. Chem.* **73,** 161–166 (1961); Hine, "Divalent Carbon," especially pp. 20–28, 42–44, 55–60, 73–78, 122–130, The Ronald Press Company, New York, 1964; and Kirmse, "Carbene Chemistry," especially pp. 26–36, 87–90, 97–106, 132–136, 163–179, 188–195, 258–272, Academic Press Inc., New York, 1964.

[308] For a review of the addition of halocarbenes, see Parham and Schweizer, *Org. Reactions* **13,** 55–90 (1963).

[309] For example, see Frey, *J. Chem. Soc.* **1962,** 2293.

[310] For a review of additions of CH_2, see Bell, *Progr. Phys. Org. Chem.* **2,** 1–61 (1964), pp. 8–27, 43–45.

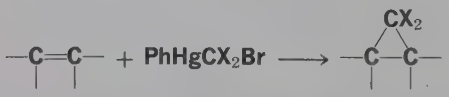
$$CHCl_3 + OH^- \text{ or } tert\text{-}BuO^- \longrightarrow \bar{C}Cl_2$$

$$Cl_3CSO_2Me + tert\text{-}BuO^- \longrightarrow \bar{C}Cl_2 \qquad \text{(Ref. 311)}$$

$$Cl_3CCOONa \xrightarrow{MeOCH_2CH_2OMe} \bar{C}Cl_2 \qquad \text{(Ref. 312)}$$

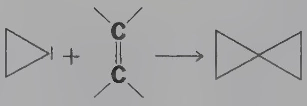
$$Cl_3CCOOEt + tert\text{-}BuO^- \longrightarrow \bar{C}Cl_2 \qquad \text{(Ref. 313)}$$

The latter method, particularly, gives high yields of dihalocyclopropanes. Another method for the preparation of dihalocyclopropanes does not involve α-elimination:[314]

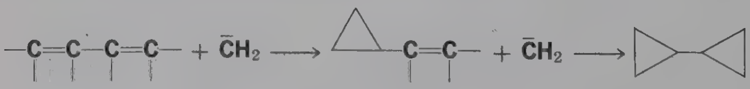


X = Cl or Br

Dihalocyclopropanes are very useful compounds which can be hydrolyzed to cyclopropanones, reduced to cyclopropanes,[315] or treated with magnesium or sodium to give allenes.[316] It is possible that cyclopropylidenes are intermediates in the latter process. Cyclopropylidenes also add to olefins to give spiropentanes:[317]



Olefins of all types may be converted to cyclopropane derivatives by this reaction. Even tetracyanoethylene, which responds very poorly to electrophilic attack, gives cyclopropane derivatives with carbenes.[318] Conjugated dienes give 1,2 addition:[319]



---

[311] Schöllkopf and Hilbert, *Angew. Chem. Intern. Ed. Engl.* **1,** 401 (1962).

[312] Wagner, Kloosterziel, and van der Ven, *Rec. trav. chim.* **80,** 740 (1961).

[313] Parham and Schweizer, *J. Org. Chem.* **24,** 1733 (1959).

[314] Seyferth, Burlitch, Minasz, Mui, Simmons, Treiber, and Dowd, *J. Am. Chem. Soc.* **87,** 4259 (1965). See also Seyferth, Simmons, and Singh, *J. Organometal. Chem.* **3,** 336 (1965).

[315] Dale and Swartzentruber, *J. Org. Chem.* **24,** 955 (1959).

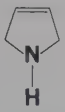
[316] Doering and LaFlamme, *Tetrahedron* **2,** 75 (1958).

[317] Jones, *J. Am. Chem. Soc.* **82,** 6200 (1960).

[318] Cairns and McKusick, *Angew. Chem.* **73,** 520 (1961).

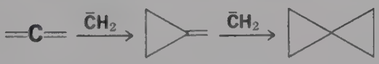
[319] Woodworth and Skell, *J. Am. Chem. Soc.* **79,** 2542 (1957).

Addition of a second mole gives bicyclopropyl derivatives.[320] 1,4 addition has also been reported. Franzen has obtained 6 to 10% cyclopentene from butadiene and carbene,[321] but this may have arisen from rearrangement of vinylcyclopropane, the 1,2 product.[322] However, nitrene, $\text{H—}\bar{\text{N}}|$, adds 1,4 (addition to butadiene gives **85**),[323] and 1,2 addition has not been observed,

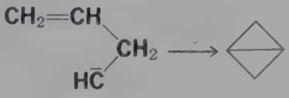


85

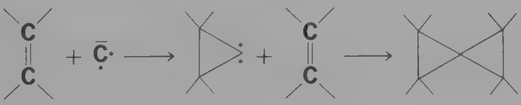
except at 4°K.[324] In the addition of carbenes to unsymmetrical dienes, that double bond is attacked first which has a larger number of alkyl groups, since that makes it more susceptible to electrophilic attack. Allenes react with carbenes to give cyclopropanes with exocyclic unsaturation:[325]



A second mole gives spiro compounds.[326] In fact, any size ring with an exocyclic double bond may be converted by a carbene to a spiro compound.[327] Allylcarbene gives internal addition, forming bicyclobutane:[328]



Spiropentanes are also formed upon reaction of olefins with atomic carbon aged on a paraffin hydrocarbon surface at −196°:[329]



The first addition is stereospecific and the second nonstereospecific, in accord with the $2s^22p_x{}^12p_y{}^1$ outer-shell configuration for the ground state of carbon.

---

[320] Orchin and Herrick, *J. Org. Chem.* **24,** 139 (1959); Nakapetyán, Safonova, and Kazanskii, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1962,** 840; Skattebøl, *J. Org. Chem.* **29,** 2951 (1964).

[321] Franzen, *Chem. Ber.* **95,** 571 (1962).

[322] Frey, *Trans. Faraday Soc.* **58,** 516 (1962).

[323] Appel and Büchner, *Angew. Chem. Intern. Ed. Engl.* **1,** 332 (1962).

[324] Jacox and Milligan, *J. Am. Chem. Soc.* **85,** 278 (1963).

[325] Ball and Landor, *Proc. Chem. Soc.* **1961,** 246.

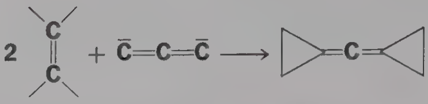
[326] Skattebøl, *Tetrahedron Letters* **1965,** 2175.

[327] See, for example, Funakubo, Moritani, Murahashi, and Tuji, *Tetrahedron Letters* **1962,** 539.

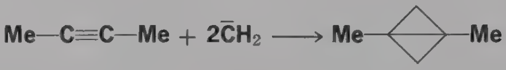
[328] Lemal, Menger, and Clark, *J. Am. Chem. Soc.* **85,** 2529 (1963).

[329] Skell and Engel, *J. Am. Chem. Soc.* **88,** 3749 (1966).

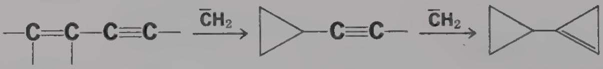
The C_3 species which is found in carbon vapor (p. 161) gives bisethanoallenes:[330]



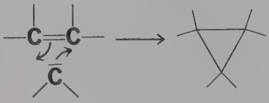
Triple-bond compounds react with carbenes to give cyclopropenes, except that in the case of acetylene itself, the cyclopropenes first formed cannot be isolated because they rearrange to allenes.[331] Cyclopropenones (p. 49) are obtained by hydrolysis of dihalocyclopropenes.[332] It has proved possible to add two moles of a carbene to an alkyne, to give a bicyclobutane:[333]



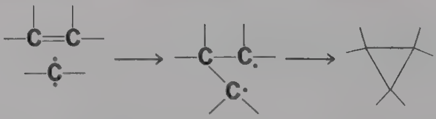
With conjugated enynes, initial attack is at the double bond, but a second mole can be added:[334]



Carbenes are electrophiles, and, in accord with this, electron-donating substituents on the olefin increase the rate of the reaction, and electron-withdrawing groups decrease it.[335] As discussed on page 160 carbenes in the singlet state (which is the most common state) react stereospecifically and cis,[336] probably by a one-step mechanism, similar to mechanism *a* of reactions **5-34** and **5-35:**



Carbenes in the triplet state react nonstereospecifically,[337] probably by a diradical mechanism, similar to mechanism *b* of reactions **5-34** and **5-35:**



---

[330] Skell, Wescott, Goldstein, and Engel, *J. Am. Chem. Soc.* **87,** 2829 (1965).

[331] Frey, *Chem. Ind. (London)* **1960,** 1266.

[332] Vol'pin, Koreshkov, and Kursanov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1959,** 535.

[333] Doering and Coburn, *Tetrahedron Letters* **1965,** 991. Also see Mahler, *J. Am. Chem. Soc.* **84,** 4600 (1962).

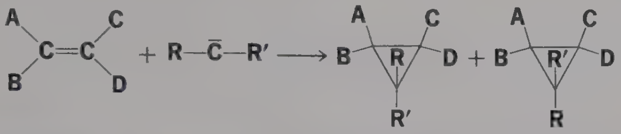
[334] D'yakanov and Danilkina, *J. Gen. Chem. USSR* **32,** 994 (1962), **34,** 738 (1964).

[335] Skell and Garner, *J. Am. Chem. Soc.* **78,** 5430 (1956); Doering and Henderson, *J. Am. Chem. Soc.* **80,** 5274 (1958).

[336] Woodworth and Skell, *J. Am. Chem. Soc.* **81,** 3383 (1959).

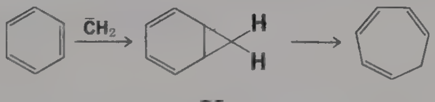
[337] Skell and Klebe, *J. Am. Chem. Soc.* **82,** 247 (1960).

For carbenes of the type R—C—R′ there is another aspect of stereochemistry. When these species are added to all but symmetrical olefins, two isomers are possible, even if the four groups originally on the double-bond carbons maintain their configurations:



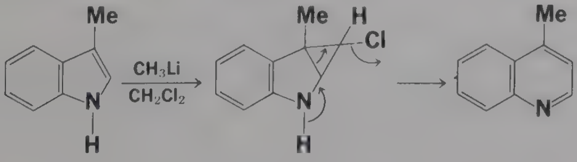
Most studies have been carried out on monosubstituted carbenes ($R' = H$), and the data so far indicate that when R = carbalkoxyl, alkoxyl, and aroxyl, the R group generally appears on the less substituted side, while, when R = alkyl, aryl, chloro, or arylthio, the R group generally is found on the more substituted side.[338]

Carbenes are so reactive that they add to the "double bonds" of aromatic rings. The products are usually not stable and rearrange to give ring expansion. Carbene reacts with benzene to give cycloheptatriene:[339]



86

but most carbenes are not reactive enough to add to benzene. The norcaradiene intermediate (**86**) cannot be isolated, though the corresponding compound in the case where $C(CN)_2$ is added to benzene has been isolated.[340] In this case, heating of the intermediate did not give the seven-membered ring, perhaps because CN^- is such a poor leaving group, but instead gave $PhCH(CN)_2$. With CH_2, insertion is a major side reaction, and, for example, benzene gives toluene as well as cycloheptatriene. A method of adding CH_2 to benzene rings without the use of free carbene is to catalyze decomposition of CH_2N_2 in the aromatic compound as solvent with CuCl or CuBr.[341] By this method better yields of cycloheptatrienes are obtained without insertion side products. CHCl is active enough to add to benzene, but dihalocarbenes do not add to benzene or toluene, only to rings with greater electron density. Pyrroles and indoles may be expanded, respectively, to pyridines and quinolines, by treatment with halocarbenes, for example:



87

---

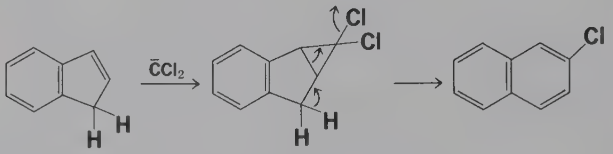
[338] Closs, Moss, and Coyle, *J. Am. Chem. Soc.* **84,** 4985 (1962); Moss, *J. Org. Chem.* **30,** 3261 (1965).

[339] Doering and Knox, *J. Am. Chem. Soc.* **75,** 297 (1951).

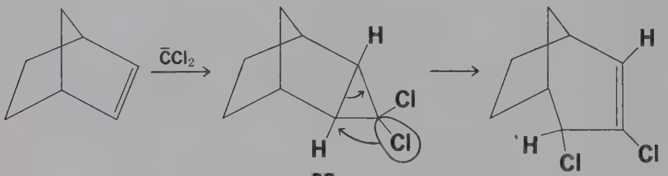
[340] Ciganek, *J. Am. Chem. Soc.* **89,** 1454 (1967).

[341] Müller and Fricke, *Ann.* **661,** 38 (1963); Müller, Kessler, Fricke, and Kiedaisch, *Ann.* **675,** 63 (1964).

The intermediate in this reaction (**87**) has not been isolated, but it has been trapped, as the N-acetate,[342] which with alcoholic KOH gives the quinoline product. In the reaction between indene and CCl_2, the intermediate has been isolated:[343]



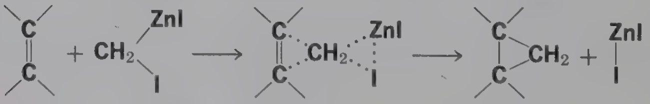
In such cases a side reaction which sometimes occurs is expansion of the *six-membered* ring. Ring expansion may occur even with nonaromatic compounds, when the driving force is supplied by relief of strain, e.g.,



88

88 is so strained that it rearranges,[344] though it has been isolated.[345]

As previously mentioned, free carbene is not very useful for additions to double and triple bonds, since it gives too many side products. The *Simmons-Smith procedure* accomplishes the same result, but without a free carbene intermediate and without insertion side products. This procedure involves treatment of the double or triple bond compound with CH_2I_2 and Zn-Cu and leads to cyclopropane derivatives in good yields.[346] The actual attacking species is an organozinc intermediate, probably $(ICH_2)_2Zn{\cdot}ZnI_2$. This intermediate is stable enough for solutions of it to be isolable.[347] These solutions give CH_2I_2 when treated with I_2 (reaction **2-19,** p. 473), and CH_3I when treated with H_2O (reaction **2-14,** p. 470). The stereochemistry of the addition is cis, and a concerted mechanism is likely, perhaps[348]



---

[342] Dobbs, *Chem. Commun.* **1965,** 56.

[343] Parham and Reiff, *J. Am. Chem. Soc.* **77,** 1177 (1955); Parham, Reiff, and Swartzentruber, *J. Am. Chem. Soc.* **78,** 1437 (1956).

[344] Bergman, *J. Org. Chem.* **28,** 2210 (1963).

[345] Moore, Moser, and LaPrade, *J. Org. Chem.* **28,** 2201 (1963); DeSelms and Combes, *J. Org. Chem.* **28,** 2206 (1963).

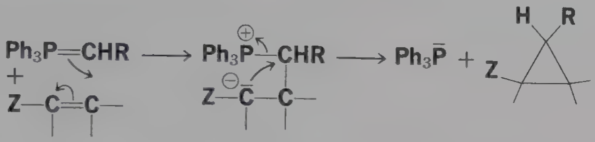
[346] Simmons and Smith, *J. Am. Chem. Soc.* **81,** 4256 (1959). The method was improved by Shank and Shechter, *J. Org. Chem.* **24,** 1525 (1959), and further improved by LeGoff, *J. Org. Chem.* **29,** 2048 (1964). Also see Wittig and Wingler, *Chem. Ber.* **97,** 2139, 2145 (1964); Seyferth, Eisert, and Todd, *J. Am. Chem. Soc.* **86,** 121 (1964); and Furukawa, Kawabata, and Nishimura, *Tetrahedron Letters* **1966,** 3353.

[347] Blanchard and Simmons, *J. Am. Chem. Soc.* **86,** 1337 (1964).

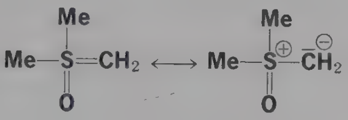
[348] Simmons, Blanchard, and Smith, *J. Am. Chem. Soc.* **86,** 1347 (1964).

With the Simmons-Smith procedure, as with free carbenes, conjugated dienes give 1,2 addition.[349]

Many substituted cyclopropanes have been made by treatment of olefins with HCWZX, where W = H, R, Ar, Cl, or COOR; Z = COOR, CN, or COAr, and X = Cl or Br.[350] This is also a cis addition. Still another method involves treatment of Michael-type olefins with phosphorus ylides:[351]



A similar reaction has been performed with the sulfur ylide **89**.[352] The reactions with ylides are, of course, nucleophilic addition. When compounds

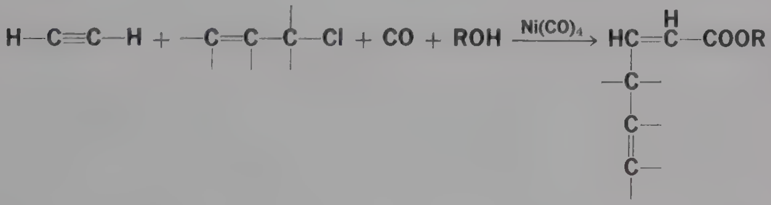


89

like $BrCCl_3$ or H_2CCl_2 are treated with butyllithium, then CCl_2 or CHCl (respectively) adds to olefins. Carbenes are probably not intermediates.

OS **41**, 72, 76.

5-38 Carboxylation of halides with insertion of acetylene (addition of carbon, carbon)



Treatment of acetylene at ordinary temperatures and pressures with an allylic halide, CO, an alcohol (or water), and a $Ni(CO)_4$ catalyst results in the preparation of an α,β:δ,ε-bis-unsaturated ester (or acid).[353] Substituted acetylenes yield cyclization products, both five- and six-membered, by reaction of the initial product with additional CO, for example,[354]

---

[349] Overberger and Halek, *J. Org. Chem.* **28,** 867 (1963).

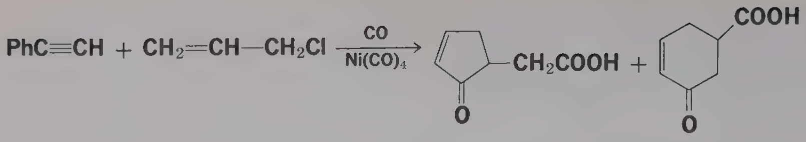
[350] Warner, *J. Org. Chem.* **24,** 1536 (1959); McCoy, *J. Org. Chem.* **25,** 2078 (1960), *J. Am. Chem. Soc.* **84,** 2246 (1962).

[351] Bestmann and Eng, *Angew. Chem. Intern. Ed. Engl.* **1,** 116 (1962).

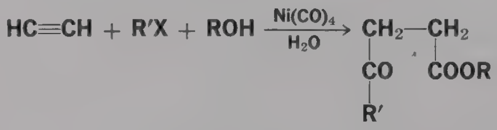
[352] Truce and Badiger, *J. Org. Chem.* **29,** 3277 (1964); Corey and Chaykovsky, *J. Am. Chem. Soc.* **87,** 1353 (1965).

[353] Chiusoli, *Angew. Chem.* **72,** 74 (1960).

[354] Chiusoli, Bottaccio, and Venturello, *Tetrahedron Letters* **1965,** 2875.



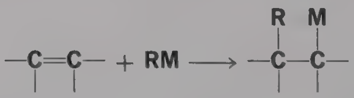
In the absence of water, the products are different.[355] The halide may be any of various primary or secondary allylic halides which do not have electron-withdrawing groups on the double-bond carbons. With respect to the halide, this is an S_N1 reaction, and allylic shifts are found. Secondary allylic halides give almost exclusively the allylic-shift product. The same products are obtained when $-\underset{|}{C}=\underset{|}{C}-\overset{|}{\underset{|}{C}}-COCl$ are used; that is, CO splits out before the ion reacts further. On the other hand, when ordinary alkyl halides or aryl halides are used, another CO is found in the product and the double bond is hydrogenated:[356]



$$HC{\equiv}CH + R'X + ROH \xrightarrow[H_2O]{Ni(CO)_4} \underset{\underset{R'}{|}}{\underset{CO}{\underset{|}{CH_2}}}-\underset{COOR}{\underset{|}{CH_2}}$$

Therefore, when $-\underset{|}{C}=\underset{|}{C}-\overset{|}{\underset{|}{C}}-X$ or $-\underset{|}{C}=\underset{|}{C}-\overset{|}{\underset{|}{C}}-COX$ is used, the allylic cation (perhaps complexed to the nickel)[357] is the positive attacking species; while with RX or ArX it is RCO^+ (acylium ion). The negative attacking entity in either case is CO. Which species makes the initial attack (that is, whether the addition is electrophilic or nucleophilic) is not certain, but in view of the susceptibility of acetylene to nucleophilic attack, it is probably CO.

5-39 Addition of organometallic compounds (addition of carbon, metal)



$$-\underset{|}{C}=\underset{|}{C}- + RM \longrightarrow -\overset{\overset{R}{|}}{\underset{|}{C}}-\overset{\overset{M}{|}}{\underset{|}{C}}-$$

The addition of organometallic compounds to double bonds is important only for alkyllithiums. Grignard reagents in general add only to double bonds susceptible to nucleophilic attack: fluoroolefins, fulvenes, etc., though it has been shown that active Grignard reagents (allyl, benzyl) can add to double bonds of allylic and homoallylic alcohols.[358]

---

[355] Cassar and Chiusoli, *Tetrahedron Letters* **1965,** 3295, **1966,** 2805.

[356] Chiusoli, Merzoni, and Mondelli, *Tetrahedron Letters* **1964,** 2777.

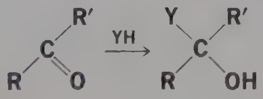
[357] Dubini, Chiusoli, and Montino, *Tetrahedron Letters* **1963,** 1591.

[358] Eisch and Husk, *J. Am. Chem. Soc.* **87,** 4194 (1965); Chérest, Felkin, Frajerman, Lion, Roussi, and Swierczewski, *Tetrahedron Letters* **1966,** 875.

CHAPTER SIXTEEN
Addition to Carbon-Hetero Multiple Bonds

MECHANISM AND REACTIVITY

The reactions considered in this chapter involve addition to the carbon-oxygen, carbon-nitrogen, and carbon-sulfur double bonds and to the carbon-nitrogen triple bond. The mechanistic study of these reactions is much simpler than of the additions to carbon-carbon multiple bonds considered in Chapter 15.[1] Most of the questions which concerned us there either do not arise here or can be answered very simply. Since these bonds are strongly polar, with the carbon always the positive end (except for isonitriles, see p. 724), there is never any doubt about *orientation* of unsymmetrical addition. Negative attacking species always go to the carbon, and positive ones to the oxygen, nitrogen, or sulfur. The *stereochemistry* of addition is not generally a factor, because it is not normally possible to determine whether the addition is cis or trans. In addition of YH to a ketone, for example,



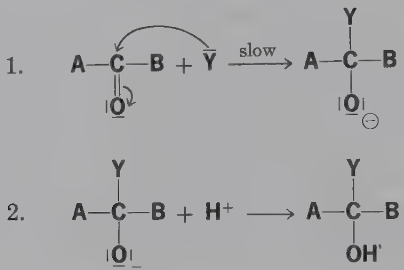
the product has an asymmetric carbon, but unless there is asymmetry in R or R′, or unless YH is optically active, the product must be a racemic mixture, and there is no way to tell from its steric nature whether the addition of Y and H was cis or trans. The same holds true for C=N and C=S bonds, since in none of these cases can asymmetry be present at the hetero atom. The stereochemistry of additions of a single YH to the carbon-nitrogen triple bond could be investigated, since the product can exist in syn and anti forms (p. 95), but these reactions are not very important. Of course if R or R′ *is* optically active, then a racemic mixture will not always arise, and the stereochemistry of addition can be studied in such cases. Cram's rule (p. 90) allows us to predict in many cases the direction of attack of Y. Another such rule is Prelog's rule.[2] However, even in this type of study, the relative directions of attack of Y and H are not determined, but only the direction of attack of Y with respect to the rest of the substrate molecule.

---

[1] For a discussion, see Jencks, *Progr. Phys. Org. Chem.* **2**, 63–118 (1964).

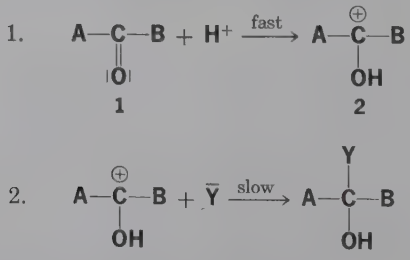
[2] Prelog, *Helv. Chim. Acta* **36**, 308 (1953); for a discussion of these rules, see Eliel, "The Stereochemistry of Carbon Compounds," pp. 68–74, McGraw-Hill Book Company, New York, 1962. For a review of the stereochemistry of addition to cyclic ketones, see Kamernitskii and Akhrem, *Tetrahedron* **18**, 705–750 (1962); *Russ. Chem. Rev.* **30**, 43–61 (1961). (Both of these references contain the same review.)

Not only are questions of orientation and stereochemistry not of great importance in the study of these mechanisms, but the picture is further simplified by the fact that free-radical additions to carbon-hetero double bonds are rare.[3] The principal question remaining is which attacks first, the positive or negative species. In most cases it is the negative species, and these reactions are regarded as *nucleophilic additions,* which may be represented thus (for the C=O bond, analogously for the others):



The positive species shown in step 2 is the proton. In almost all of the reactions considered in this chapter the positive attacking atom is either hydrogen or carbon. It may be noted that step 1 is exactly the same as step 1 of the tetrahedral mechanism of nucleophilic substitution at a carbonyl carbon (p. 274), and it might be expected that substitution would compete with addition. However, this is seldom the case. When A and B are H, R, or Ar, the substrate is an aldehyde or ketone, and these almost never undergo substitution, owing to the extremely poor nature of H, R, and Ar as leaving groups. For acids and their derivatives (B = OH, OR, NH_2, etc.) addition is seldom found, because these are much better leaving groups. It is thus the nature of A and B which determines whether a nucleophilic attack at a carbon-hetero multiple bond will lead to substitution or addition.

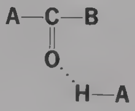
As is the case in the tetrahedral mechanism, it is also possible for the positive species to attack first, in which case it goes to the hetero atom. This species is most often a proton, and the mechanism is as follows:



---

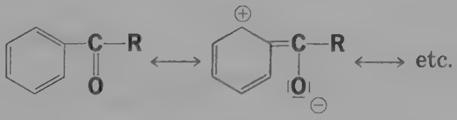
[3] For an example, see Kaplan, *J. Am. Chem. Soc.* **88**, 1833 (1966).

The two mechanisms are not usually regarded as being very different, and in each case the rate-determining step is usually the one involving nucleophilic attack. It may be observed that many of these reactions may be catalyzed by both acids and bases. Bases can catalyze the reaction by converting a reagent of the form YH to the more powerful nucleophile Y^- (see p. 288). Acids may catalyze it by converting the substrate (for example, **1**) to an ion (**2**) in which the positive charge on the carbon is greatly increased, thus making it more attractive to nucleophilic attack. The latter type of catalysis may also take place with acids which are not so acidic that a proton is actually transferred to the substrate, but which are able to form a hydrogen bond with it:



also resulting in a decreased electron density at the carbon. Similar catalysis may also be found with metallic ions, such as Ag^+, which may act here as Lewis acids.[4]

Reactivity factors in additions to carbon-hetero multiple bonds are similar to those for the tetrahedral mechanism of nucleophilic substitution. If A and/or B are electron-donating groups, rates are decreased. Electron-attracting substituents increase rates. This means that aldehydes are more reactive than ketones. Table 1 illustrates these generalizations. Aryl groups are somewhat deactivating compared to alkyl, because of resonance, which stabilizes the substrate molecule but is lost on going to the intermediate:



Double bonds in conjugation with the carbon-hetero multiple bond also lower addition rates, for similar reasons, but, more important, may provide competition from 1,4 addition (p. 568). Steric factors are also quite important. Highly hindered ketones like hexamethylacetone and dineopentyl ketone[5] either do not undergo many of these reactions or require extreme conditions.

REACTIONS

Many of the reactions in this chapter are simple additions to carbon-hetero multiple bonds, with the reaction ending as soon as the two groups have been

---

[4] Toromanoff, *Bull. Soc. chim. France* **1962,** 1190.

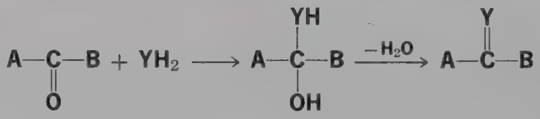
[5] Liberman and Vasina, *J. Gen. Chem. USSR* **32,** 3179 (1962).

TABLE 1. Percentage yields in the Perkin reaction (6-42) run on benzaldehydes substituted in the ring by methyl and chloro[6]

R *in* RCHO	*Yield, %*
Phenyl	45–50
2-Methylphenyl	15
3-Methylphenyl	23
4-Methylphenyl	33
2,6-Dimethylphenyl	0
2-Chlorophenyl	71
3-Chlorophenyl	63
4-Chlorophenyl	52
2,6-Dichlorophenyl	82

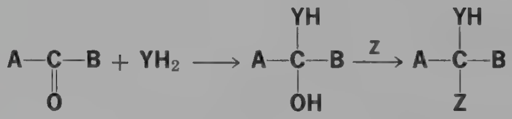
added. But in many other cases subsequent reactions take place. We shall meet a number of such reactions, but most of them are of two types:

Type *A*



$$\mathrm{A{-}\underset{\underset{O}{\|}}{C}{-}B + YH_2 \longrightarrow A{-}\overset{YH}{\underset{OH}{C}}{-}B \xrightarrow{-H_2O} A{-}\overset{\overset{Y}{\|}}{C}{-}B}$$

Type *B*



$$\mathrm{A{-}\underset{\underset{O}{\|}}{C}{-}B + YH_2 \longrightarrow A{-}\overset{YH}{\underset{OH}{C}}{-}B \xrightarrow{Z} A{-}\overset{YH}{\underset{Z}{C}}{-}B}$$

In type *A*, the adduct loses water (or, in the case of addition to C=NH, ammonia, etc.), and the net result of the reaction is the substitution of C=Y for C=O (or C=NH, etc.). In type *B* there is a rapid substitution, and the OH (or NH_2, etc.) is replaced by another group Z, with Z very often being another YH moiety. This substitution is in most cases nucleophilic, since Y usually has an unshared pair, and S_N1 reactions occur very well on this type of compound (see p. 284), even when the leaving group is as poor as OH or NH_2. In this chapter we shall classify reactions according to what is initially adding to the carbon-hetero multiple bond, even if subsequent reactions take place so rapidly that it is not possible to isolate the initial adduct. It is true that this involves a certain danger, since we cannot always be sure just which reaction occurred first (e.g., reactions **6-7** and **6-17**). In such cases we shall make the assumptions which seem most reasonable from the mechanistic data at hand.

Nearly all of the reactions considered in this chapter can be reversed. In many cases we shall consider the reverse reactions with the forward ones, in the same section. The reverse of some of the other reactions are considered in other chapters. In still other cases, one of the reactions in this chapter is the reverse of another (e.g., reactions **6-2** and **6-15**). For those reactions which are reversible, the principle of microscopic reversibility (p. 204) applies.

---

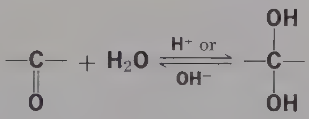
[6] Böck, Lock, and Schmidt, *Monatsh. Chem.* **64**, 399 (1934).

We shall discuss first reactions in which hydrogen or a metallic ion (or in one case phosphorus or sulfur) adds to the hetero atom, and then reactions in which carbon adds to the hetero atom. Within each group, the reactions are classified by the nature of the nucleophile. Additions to isonitriles, which are somewhat different in character, are treated at the end.

Reactions in Which Hydrogen or a Metallic Ion Adds to the Hetero Atom

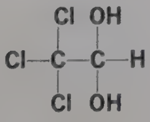
A. Attack by OH (addition of H_2O)

6-1 The addition of water to aldehydes and ketones. The formation of hydrates

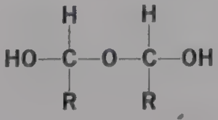


$$-\underset{\underset{\displaystyle O}{\|}}{C}- + H_2O \underset{OH^-}{\overset{H^+ \text{ or}}{\rightleftharpoons}} -\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-$$

The adduct formed upon addition of water to an aldehyde or ketone is called a *hydrate*.[6a] These compounds are usually stable only in water solution and decompose on distillation; that is, the equilibrium shifts back toward the carbonyl compound. The position of the equilibrium is greatly dependent on the structure of the hydrate. Thus, formaldehyde in water at 20° exists 99.99% in the hydrated form, while for acetaldehyde this figure is 58%, and for acetone the hydrate concentration is negligible.[7] It has been found, by exchange with ^{18}O, that the reaction with acetone is quite rapid when catalyzed by acid or base, but the equilibrium lies on the side of acetone and water.[8] Acetone hydrate *has* been shown to exist in the solid state (frozen mixtures of acetone and water).[9] Since methyl, a $+I$ group, inhibits hydrate formation, it may be expected that electron-attracting groups would have the opposite effect, and this is indeed the case. The hydrate of chloral (**3**) is a stable crystalline substance. In order for **3** to revert to chloral, OH^- or H_2O must leave, and this is rendered difficult by the electron-withdrawing character of the Cl_3C group. Other polychlorinated and polyfluorinated aldehydes and ketones, and α-keto aldehydes also form stable hydrates. Higher-molecular-weight aldehydes (for example, C_7 and



3



4

[6a] For a review, see Bell, *Advan. Phys. Org. Chem.* **4**, 1–29 (1966).

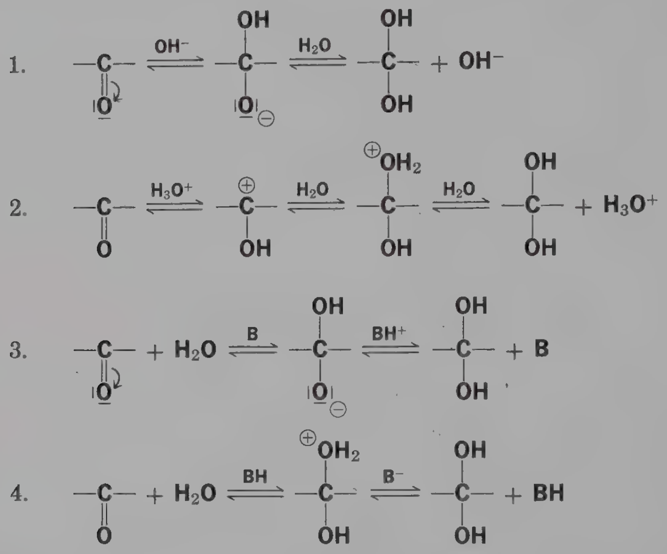
[7] Bell and Clunie, *Trans. Faraday Soc.* **48**, 439 (1952).

[8] Cohn and Urey, *J. Am. Chem. Soc.* **60**, 679 (1938).

[9] Wilson and Davidson, *Can. J. Chem.* **41**, 264 (1963).

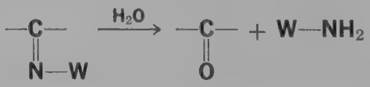
up) form solid hemihydrates (**4**), which are stable at low temperatures (near 0°) but decompose to the aldehyde and water at about 40 to 50°.[10]

The reaction is subject to both general acid and general base catalysis, so four mechanisms must be given, all of which are examples of the general mechanism discussed on page 652.[11]



Mechanisms 1 and 2 are for catalysis by OH^- and H_3O^+, respectively. Mechanisms 3 and 4 are for catalysis by other bases (B) or other acids (BH). In mechanism 3, as the H_2O attacks, the base pulls off a proton, and the net result is addition of OH^-. This can happen because the base is already hydrogen-bonded to the H_2O molecule before the attack. In mechanism 4, because HB is already hydrogen-bonded to the oxygen of the carbonyl group, it gives up a proton to the oxygen as the water attacks. In this way B and HB accelerate the reaction even beyond the extent that they form OH^- or H_3O^+ by reaction with water.

6-2 Hydrolysis of the carbon-nitrogen double bond



$$-\underset{\underset{\displaystyle N-W}{\|}}{C}- \xrightarrow{H_2O} -\underset{\underset{\displaystyle O}{\|}}{C}- + W-NH_2$$

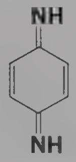
Compounds containing carbon-nitrogen double bonds may be hydrolyzed to the corresponding aldehydes or ketones. For imines (W = R or H) the hydrolysis is easy and may be carried out with water. When W = H, the imine is seldom stable enough for isolation, but hydrolysis is often done *in*

---

[10] Klass, Jensen, Blair, and Martinek, *J. Org. Chem.* **28,** 3029 (1963).

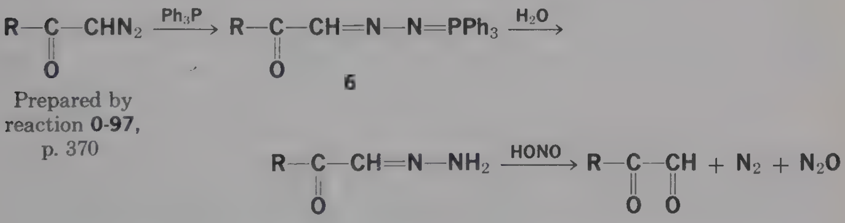
[11] Bell, Rand, and Wynne-Jones, *Trans. Faraday Soc.* **52,** 1093 (1952); Pocker, *Proc. Chem. Soc.* **1960,** 17.

situ, without isolation. Quinone imines (**5**) may be similarly hydrolyzed to quinones. The hydrolysis of Schiff bases (W = Ar) is more difficult and requires acid or basic catalysis. Oximes (W = OH), arylhydrazones (W = NHAr), and, most easily, semicarbazones (W = $NHCONH_2$) may also be hydrolyzed. Often a reactive aldehyde is added to combine with the liberated amine. Formaldehyde is generally used for this purpose, but levulinic acid is excellent for hydrolyzing oximes and arylhydrazones.[12]



5

Aldehydes and ketones may be purified by conversion to the oxime, semicarbazone, or arylhydrazone derivative (reactions **6-21** and **6-22**), which is then recrystallized and hydrolyzed back to the starting compound. Conversion of a hydrazone to an aldehyde is the key step in the transformation of a carboxylic acid to an α-keto aldehyde, a method of increasing the carbon chain by one:[13]



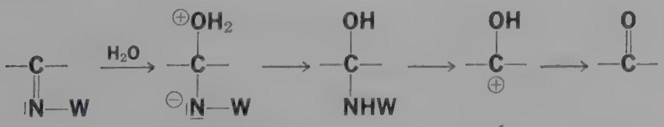
$$R-\underset{\underset{O}{\|}}{C}-CHN_2 \xrightarrow{Ph_3P} \underset{\mathbf{6}}{R-\underset{\underset{O}{\|}}{C}-CH{=}N-N{=}PPh_3} \xrightarrow{H_2O}$$

Prepared by
reaction **0-97**,
p. 370

$$R-\underset{\underset{O}{\|}}{C}-CH{=}N-NH_2 \xrightarrow{HONO} R-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}H + N_2 + N_2O$$

Direct treatment of the α-ketotriphenylphosphazine (**6**) with HONO also gives the product.

The hydrolysis of carbon-nitrogen double bonds involves initial addition of water and elimination of a nitrogen moiety:



$$-\underset{\underset{|N-W}{\|}}{C}- \xrightarrow{H_2O} -\overset{\overset{\oplus OH_2}{|}}{\underset{\underset{\ominus|\underline{N}-W}{|}}{C}}- \longrightarrow -\overset{\overset{OH}{|}}{\underset{\underset{NHW}{|}}{C}}- \longrightarrow -\overset{\overset{OH}{|}}{\underset{\oplus}{C}}- \longrightarrow -\overset{\overset{O}{\|}}{C}-$$

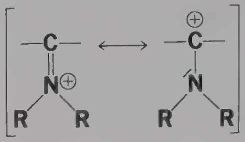
It is thus an example of reaction type *A* (p. 654). The sequence shown is generalized. In specific cases there are variations in the order of the steps, depending on acid or basic catalysis or other conditions.[14] Which step is rate-determining also depends on acidity and on the nature of W and of the groups connected to the carbonyl.[15] Iminium ions (**7**) would be expected to undergo hydrolysis quite readily, since there is a contributing form with a positive charge on the carbon. Indeed, they react with water at room temperature.[16] It has been proposed that acid-catalyzed hydrolysis of enamines (the last step of the Stork reaction, reaction **2-10**, p. 464) involves conversion to iminium ions:[17]

---

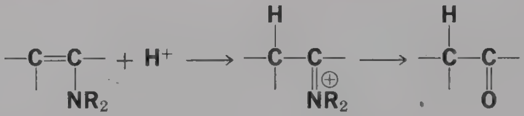
[12] DePuy and Ponder, *J. Am. Chem. Soc.* **81**, 4629 (1959).

[13] Bestmann, Klein, Göthlich, and Buckschewski, *Chem. Ber.* **96**, 2259 (1963).

[14] For example, see Reeves, *J. Am. Chem. Soc.* **84**, 3332 (1962).



7



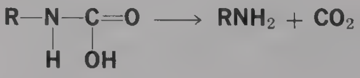
$$-\underset{|}{C}=\underset{\underset{NR_2}{|}}{C}- + H^+ \longrightarrow -\overset{\overset{H}{|}}{\underset{|}{C}}-\underset{\underset{NR_2}{\|\oplus}}{C}- \longrightarrow -\overset{\overset{H}{|}}{\underset{|}{C}}-\underset{\underset{O}{\|}}{C}-$$

OS **I,** 217, 298, 318, 381; **II,** 49, 223, 234, 284, 310, 333, 395, 519, 522; **III,** 20, 172, 626, 818; **IV,** 120; **44,** 72, 75.

6-3 Hydrolysis of isocyanates and isothiocyanates

$$R-N=C=O + H_2O \xrightarrow{OH^- \text{ or } H^+} R-NH_2 + CO_2$$

A common method for the preparation of primary amines involves the hydrolysis of isocyanates or isothiocyanates. The latter react more slowly, and more vigorous conditions are required. The reaction is catalyzed by acids or bases. In this case simple addition of water to the carbon-nitrogen double bond would give an N-substituted carbamic acid (**8**). Such compounds are unstable, however, and break down to carbon dioxide (or COS in the case of isothiocyanates) and the amine:



$$R-\underset{\underset{H}{|}}{N}-\underset{\underset{OH}{|}}{C}=O \longrightarrow RNH_2 + CO_2$$

8

In the absence of a basic catalyst, disubstituted ureas, RNHCONHR, may be obtained by a nucleophilic substitution of RNH_2 on the carbamic acid.[18]

OS **II,** 24; **IV,** 819.

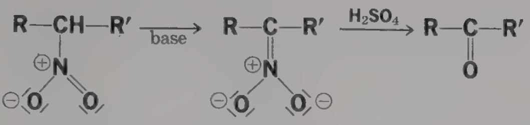
[15] Cordes and Jencks, *J. Am. Chem. Soc.* **85,** 2843 (1963).

[16] Hauser and Lednicer, *J. Org. Chem.* **24,** 46 (1959).

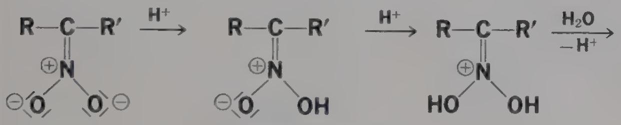
[17] Stamhuis and Maas, *J. Org. Chem.* **30,** 2156 (1965).

[18] Arnold, Nelson, and Verbang, *Chem. Rev.* **57,** 47 (1957).

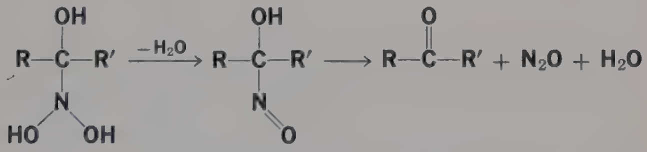
6-4 Hydrolysis of aliphatic nitro compounds



Primary or secondary aliphatic nitro compounds may be hydrolyzed, respectively, to aldehydes or ketones, by treatment of their salts with sulfuric acid. This is called the *Nef reaction.*[19] Tertiary aliphatic nitro compounds do not give the reaction, because they cannot be converted to the salt form. Like reaction **6-2**, this reaction involves hydrolysis of a carbon-nitrogen double bond. A possible mechanism is[20]



Aci form of the nitro compound



Kinetic studies show that the slow step is probably the attack of water on the protonated aci form.

The Nef reaction has been carried out with better yields and fewer side reactions by treatment of the salt of the nitro compound with $KMnO_4$.[21]

When *primary* nitro compounds are treated with sulfuric acid without previous conversion to the salt form, they give carboxylic acids. Hydroxamic acids are intermediates and may be isolated, so that this is also a method for preparing *them.* Both the Nef reaction and the hydroxamic acid process involve the aci form, and the difference in products arises from higher acidity; e.g., a difference in sulfuric acid concentration from 4 N to 31 N changes the product from the aldehyde to the hydroxamic acid.[22] The mechanism of the hydroxamic acid reaction is not known with certainty, but if higher acidity is required, then it may be that the protonated aci form of the nitro compound is further protonated. The following rationalization has been proposed:[22]

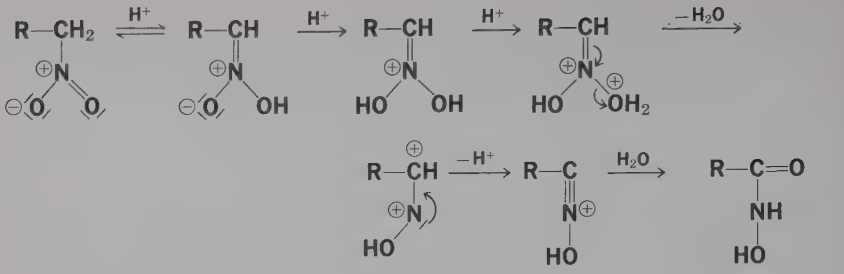
---

[19] For a review, see Noland, *Chem. Rev.* **55**, 137–155 (1955).

[20] Hawthorne, *J. Am. Chem. Soc.* **79**, 2510 (1957). A similar mechanism, but with some slight differences, was suggested earlier by van Tamelen and Thiede, *J. Am. Chem. Soc.* **74**, 2615 (1952).

[21] Shechter and Williams, *J. Org. Chem.* **27**, 3699 (1962).

[22] Kornblum and Brown, *J. Am. Chem. Soc.* **87**, 1742 (1965).

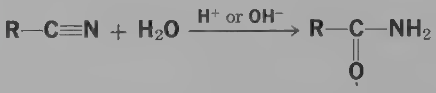


Hydroxamic acid

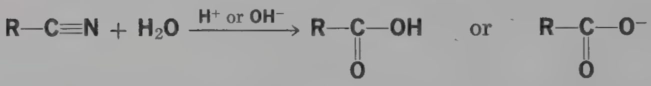
Hydrolysis of the hydroxamic acid produces the carboxylic acid.

There are no OS references, but see OS **IV,** 573, for a related reaction.

6-5 Hydrolysis of nitriles



$$R{-}C{\equiv}N + H_2O \xrightarrow{H^+ \text{ or } OH^-} R{-}\underset{\underset{O}{\|}}{C}{-}NH_2$$



$$R{-}C{\equiv}N + H_2O \xrightarrow{H^+ \text{ or } OH^-} R{-}\underset{\underset{O}{\|}}{C}{-}OH \quad \text{or} \quad R{-}\underset{\underset{O}{\|}}{C}{-}O^-$$

Nitriles may be hydrolyzed to give either amides or carboxylic acids.[23] The amide is the initial product, but since amides are also hydrolyzed with acid or basic treatment, the carboxylic acid is the more common product. There are a number of procedures for stopping at the amide stage, among them the use of concentrated H_2SO_4; acetic acid and BF_3; H_2O_2 and OH^-; and dry HCl followed by H_2O. The same result may also be obtained by use of water and nickel,[24] or MnO_2 in methylene chloride,[25] in which cases no acid or base is used.

The hydrolysis of nitriles to carboxylic acids is one of the best methods for the preparation of these compounds. Nearly all nitriles give the reaction, with either acid or basic catalysts. The sequences

$RX + NaCN \longrightarrow RCN \longrightarrow RCOOH$ (reaction **0-88,** p. 361)

$RCHO + HCN \longrightarrow RCH(OH)CN \longrightarrow RCH(OH)COOH$ (reaction **6-47**)

$RCHO + NaCN + NH_4Cl \longrightarrow RCH(NH_2)CN \longrightarrow RCH(NH_2)COOH$ (reaction **6-48**)

are very common. The latter two sequences are often carried out without isolation of the cyanide intermediates.

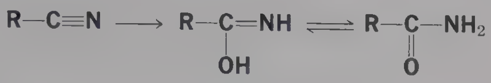
---

[23] For a review, see Zil'berman, *Russ. Chem. Rev.* **31,** 615–633 (1962).

[24] Watanabe, *Bull. Chem. Soc. Japan* **32,** 1280 (1959), **37,** 1325 (1964).

[25] Cook, Forbes, and Kahn, *Chem. Commun.* **1966,** 121.

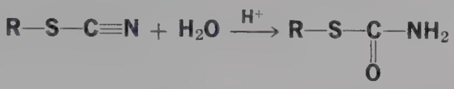
The first addition product is **9**, which tautomerizes to the amide.



$$R{-}C{\equiv}N \longrightarrow R{-}\underset{\substack{|\\ OH}}{C}{=}NH \rightleftharpoons R{-}\underset{\substack{\|\\ O}}{C}{-}NH_2$$

9

Thiocyanates may be converted to thiocarbamates, in a similar reaction:[26]

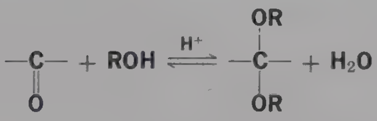


$$R{-}S{-}C{\equiv}N + H_2O \xrightarrow{H^+} R{-}S{-}\underset{\substack{\|\\ O}}{C}{-}NH_2$$

OS **I,** 21, 131, 201, 289, 298, 321, 336, 406, 436, 451; **II,** 29, 44, 292, 376, 512, 586, 588; **III,** 34, 66, 84, 88, 114, 221, 557, 560, 615, 851; **IV,** 58, 93, 496, 506, 664, 760, 790; **40,** 11. Also see OS **III,** 609; **IV,** 359, 502.

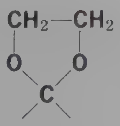
B. Attack by OR (addition of ROH)

6-6 The addition of alcohols to aldehydes and ketones



$$-\underset{\substack{\|\\ O}}{C}- + ROH \overset{H^+}{\rightleftharpoons} -\overset{\substack{OR\\ |}}{\underset{\substack{|\\ OR}}{C}}- + H_2O$$

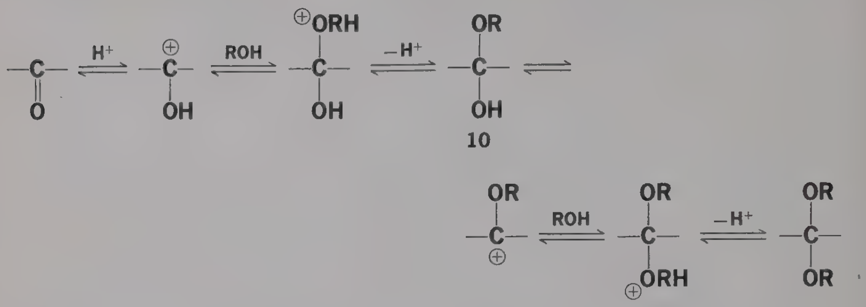
Acetals and ketals are formed by treatment of aldehydes and ketones, respectively, with alcohols in the presence of acid catalysts. This is a reversible reaction, and acetals and ketals may be hydrolyzed by treatment with acid (reaction **0-7**, p. 306). With small unbranched aldehydes and ketones the equilibrium lies to the right. If it is desired to prepare acetals or ketals of larger molecules, the equilibrium must be shifted, usually by removal of water. The reaction in neither direction is catalyzed by bases, and so acetals and ketals are quite stable to bases, though they are easily hydrolyzed by acids. This makes this reaction a useful method of protection of aldehyde or ketone functions from attack by bases. The reaction is of wide scope, and most aldehydes and ketones may be converted to acetals and ketals, though the process is more difficult with ketones. 1,2-Glycols and 1,3-glycols form cyclic acetals and ketals, e.g.,



---

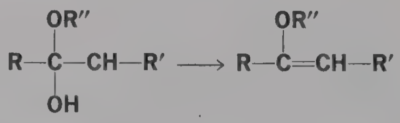
[26] Zil'berman and Lazaris, *J. Gen. Chem. USSR* **33,** 1012 (1963).

The mechanism involves initial formation of a *hemiacetal* (**10**):



Hemiacetals react rapidly by the S_N1 mechanism to give acetals (p. 284). The conversion of the hemiacetal to the acetal is actually an example of reaction **0-20** (p. 317). The mechanism has been mostly studied from the acetal side. Among the facts supporting it are[27] (1) the reaction proceeds with *specific* H_3O^+ catalysis (see p. 226); (2) it is faster in D_2O; (3) optically active ROH are not racemized; (4) even with *tert*-butyl alcohol the R—O bond does not cleave, as shown by the use of ^{18}O labeling.[28]

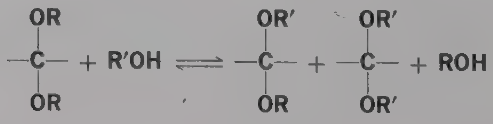
If the original aldehyde or ketone has an α hydrogen, then it is possible for water to split out in that way, and enol ethers may be prepared in this manner:



$$R-\underset{OH}{\overset{OR''}{C}}-CH-R' \longrightarrow R-\overset{OR''}{C}=CH-R'$$

Hemiacetals themselves are no more stable than the corresponding hydrates (reaction **6-1**). As with hydrates, hemiacetals of polychloro and polyfluoro aldehydes and ketones may be quite stable.

When acetals or ketals are treated with an alcohol of higher molecular weight than the one already there, it is possible to get a *transacetalation:*



$$-\underset{OR}{\overset{OR}{C}}- + R'OH \rightleftharpoons -\underset{OR}{\overset{OR'}{C}}- + -\underset{OR'}{\overset{OR'}{C}}- + ROH$$

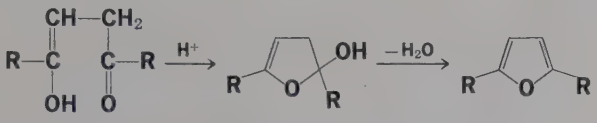
In the equilibrium mixture are present three acetals and two alcohols, and in order for the reaction to be useful, a way must be found to shift the equilibria in the desired directions.[29] 1,4-Diketones give furans when treated with acids. This is actually an example of an intramolecular addition of an alcohol to a ketone, since it is the enol form which adds:

---

[27] See Long and Paul, *Chem. Rev.* **57,** 935 (1957).

[28] Cawley and Westheimer, *Chem. Ind.* (*London*) **1960,** 656.

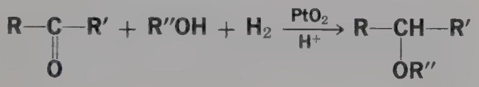
[29] Juvet and Chiu, *J. Am. Chem. Soc.* **83,** 1560 (1961).



Formic acid reacts with alcohols to give orthoformates.

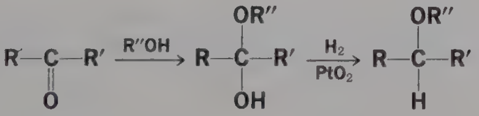
OS **I,** 1, 298, 364, 371; **II,** 137; **III,** 123, 387, 502, 536, 644, 731, 800; **IV,** 21, 479, 679; **40,** 41; **42,** 1, 34. Also see OS **IV,** 558, 588; **42,** 14.

6-7 Reductive alkylation of alcohols



$$\mathrm{R{-}\underset{\overset{\|}{O}}{C}{-}R' + R''OH + H_2 \xrightarrow[H^+]{PtO_2} R{-}\underset{\overset{|}{OR''}}{CH}{-}R'}$$

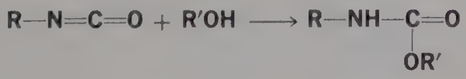
Aldehydes and ketones may be converted to ethers by hydrogenation in alcoholic acid, in the presence of platinum oxide.[30] The process may formally be regarded as addition of ROH to give a hemiacetal, followed by hydrogenolysis of the OH:



$$\mathrm{R{-}\underset{\overset{\|}{O}}{C}{-}R' \xrightarrow{R''OH} R{-}\overset{OR''}{\underset{OH}{C}}{-}R' \xrightarrow[PtO_2]{H_2} R{-}\overset{OR''}{\underset{H}{C}}{-}R'}$$

In this respect it is similar to reaction **6-16.**

6-8 The addition of alcohols to isocyanates



$$\mathrm{R{-}N{=}C{=}O + R'OH \longrightarrow R{-}NH{-}\underset{\overset{|}{OR'}}{C}{=}O}$$

Substituted urethans (carbamates) are prepared when isocyanates are treated with alcohols. This is an excellent reaction, of wide scope, and gives good yields. The carbamates are often used as derivatives of the alcohols. Cyanic acid (HNCO) gives unsubstituted urethans. Polyurethans are made by combining compounds with two NCO groups with compounds containing two OH groups. Isothiocyanates similarly give thiourethans (RNHCSOR′), though they react slower than the corresponding isocyanates.

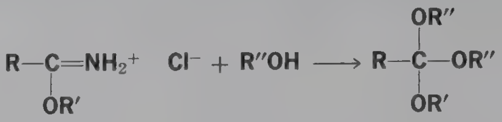
The details of the mechanism are poorly understood,[31] though the oxygen of the alcohol is certainly attacking the carbon of the isocyanate. Hydrogen bonding complicates the kinetic picture.

OS **I,** 140.

[30] Verzele, Acke, and Anteunis, *J. Chem. Soc.* **1963,** 5598.

[31] See, for example, Robertson and Stutchbury, *J. Chem. Soc.* **1964,** 4000.

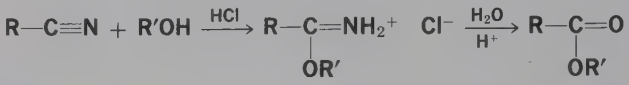
6-9 The reaction between imino ester salts and alcohols



$$\underset{\substack{|\\ OR'}}{R-C=NH_2^+}\quad Cl^- + R''OH \longrightarrow R-\overset{\substack{OR''\\ |}}{\underset{\substack{|\\ OR'}}{C}}-OR''$$

Imino ester salts (prepared by reaction **6-10**) react with alcohols to give ortho esters. The reaction gives good yields.

6-10 Alcoholysis of nitriles



$$R-C\equiv N + R'OH \xrightarrow{HCl} R-\underset{\substack{|\\ OR'}}{C}=NH_2^+\quad Cl^- \xrightarrow[H^+]{H_2O} R-\underset{\substack{|\\ OR'}}{C}=O$$

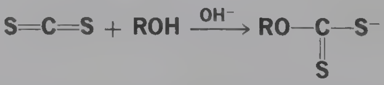
The addition of dry HCl to a mixture of a nitrile and an alcohol, in the absence of water, leads to the hydrochloride salt of an imino ester. This reaction is called the *Pinner synthesis.*[32] The salt may be converted to the free imino ester by treatment with a weak base such as sodium bicarbonate, or it may be hydrolyzed with water and an acid catalyst to the corresponding carboxylic ester. If the latter is desired, water may be present from the beginning, in which case aqueous HCl may be used and the necessity for adding gaseous HCl eliminated. Imino esters may also be prepared from nitriles with basic catalysts.[33]

This reaction is of broad scope and is good for aliphatic, aromatic, and heterocyclic R and for nitriles with oxygen-containing functional groups. The application of the reaction to nitriles containing a carboxyl group constitutes a good method for the synthesis of mono esters of dicarboxylic acids with the desired group esterified and with no diester or diacid present.

ROH may also be added to nitriles in another manner (reaction **6-54**).

OS **I**, 5, 270; **II**, 284, 310; **IV**, 645.

6-11 The formation of xanthates

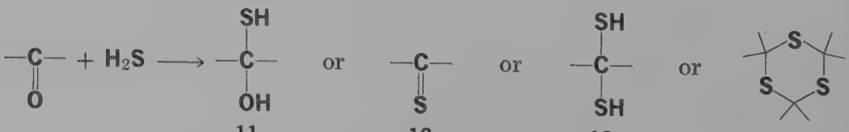


$$S=C=S + ROH \xrightarrow{OH^-} RO-\underset{\substack{\|\\ S}}{C}-S^-$$

The addition of alcohols to carbon disulfide in the presence of hydroxide ions produces xanthates.

C. Sulfur nucleophiles

6-12 The addition of H_2S and mercaptans to carbonyl compounds



11 12 13 14

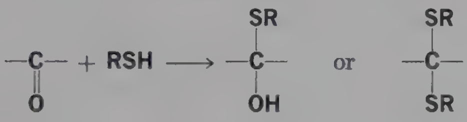
---

[32] For a review, see Zil'berman, *Russ. Chem. Rev.* **31,** 615–633 (1962), p. 621.

[33] Schaefer and Peters, *J. Org. Chem.* **26,** 412 (1961).

The addition of H_2S to an aldehyde or ketone may result in a variety of products. The most usual product is the cyclic trimer **14**.[34] α-Hydroxy thiols (**11**) can be prepared from polychloro and polyfluoro aldehydes and ketones.[35] Apparently **11** are stable only when prepared from these compounds, and not even for all of them. Thiones (**12**) can be formed from aldehydes and ketones by treatment with H_2S and HCl or $ZnCl_2$.[36] *gem*-Dithiols (**13**) are much more stable than the corresponding hydrates or α-hydroxy thiols.[37] However there are not many reports about formation of these compounds by simple addition of H_2S to carbonyl compounds. It has been accomplished by the use of H_2S under pressure,[38] and, for dibenzyl ketone, under mild conditions with HCl as a catalyst.[34] However, *gem*-dithiols may also be prepared by the treatment of imines with H_2S,[39] and this may be accomplished without isolation of the imine, if the aldehyde or ketone is treated with H_2S in the presence of ammonia or an amine.[40]

Mercaptans add to aldehydes and ketones to give stable hemimercaptals (**15**) and mercaptals (**16**). Like acetals, mercaptals are stable in the presence of bases, except that a strong base can remove the aldehyde proton, if there is one.[41] Acyl halides, treated with mercaptans, give ortho thioesters:[42]



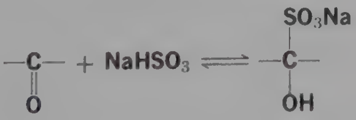
$$-\underset{\underset{\displaystyle O}{\|}}{C}- + RSH \longrightarrow -\overset{\overset{\displaystyle SR}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}- \quad \text{or} \quad -\overset{\overset{\displaystyle SR}{|}}{\underset{\underset{\displaystyle SR}{|}}{C}}-$$

15 **16**

$$RCOCl + R'SH \longrightarrow RC(SR')_3$$

OS **II,** 610; **IV,** 927. Also see OS **III,** 332; **IV,** 967.

6-13 Formation of bisulfite addition products



$$-\underset{\underset{\displaystyle O}{\|}}{C}- + NaHSO_3 \rightleftharpoons -\overset{\overset{\displaystyle SO_3Na}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-$$

Bisulfite addition products are formed from aldehydes, methyl ketones, cyclic ketones, and isocyanates, upon treatment with sodium bisulfite. The reaction is reversible and is useful for the purification of the starting compounds, since the addition products are soluble in water, and many of the impurities are not.

---

[34] Campaigne and Edwards, *J. Org. Chem.* **27,** 3760 (1962).

[35] Harris, *J. Org. Chem.* **25,** 2259 (1960).

[36] For a review, see Mayer, Morganstern, and Fabian, *Angew. Chem. Intern. Ed. Engl.* **3,** 277–286 (1964).

[37] For a review of the preparation of *gem*-dithiols, see Mayer, Hiller, Nitzschke, and Jentzsch, *Angew. Chem. Intern. Ed. Engl.* **2,** 370 (1963).

[38] Cairns, Evans, Larchar, and McKusick, *J. Am. Chem. Soc.* **74,** 3982 (1952).

[39] Magnusson, *Acta Chem. Scand.* **16,** 1536 (1962), **17,** 273 (1963).

[40] Jentzsch, Fabian, and Mayer, *Chem. Ber.* **95,** 1764 (1962).

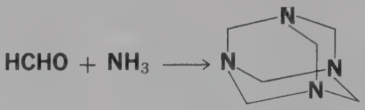
[41] Truce and Roberts, *J. Org. Chem.* **28,** 961 (1963).

[42] Rinzema, Stoffelsma, and Arens, *Rec. trav. chim.* **79,** 354 (1959).

OS **I**, 241, 336; **III**, 438; **IV**, 903; **43**, 25.

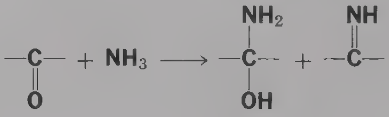
D. Attack by NH_2, NHR, or NR_2 (addition of NH_3, RNH_2, R_2NH)

6-14 The addition of ammonia to aldehydes and ketones



17

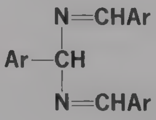
The addition of ammonia to aldehydes or ketones does not generally give useful products. According to the pattern followed by analogous nucleophiles, the initial products would be expected to be *hemiaminals* (also called "aldehyde ammonias") (**18**) and/or imines (**19**):



$$-\underset{\underset{O}{\|}}{C}- + NH_3 \longrightarrow -\overset{NH_2}{\underset{OH}{C}}- + -\overset{\overset{NH}{\|}}{C}-$$

18 **19**

However, these compounds are generally unstable. Imines with a hydrogen on the nitrogen spontaneously polymerize and have never been isolated in this reaction, though they have been shown to form, spectrophotometrically.[43] Stable hemiaminals may be prepared from polychlorinated and polyfluorinated aldehydes and ketones. Aside from these, when stable compounds *are* prepared in this reaction, they are the result of combinations and condensations of one or more molecules of **18** and/or **19** with each other or with additional molecules of ammonia or carbonyl compound. The most important example of such a product is hexamethylenetetramine (**17**), prepared from ammonia and formaldehyde. Analogs of this compound have been prepared from aromatic aldehydes and ammonium carbonate.[44] Aromatic aldehydes give hydrobenzamides (**20**) derived from three molecules of aldehyde and two



$$Ar-\overset{N=CHAr}{\underset{N=CHAr}{CH}}$$

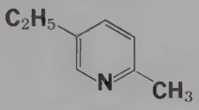
20

---

[43] McLeod and Crowell, *J. Org. Chem.* **26,** 1094 (1961).

[44] Kamal, Ahmad, and Qureshi, *Tetrahedron* **19,** 869 (1963).

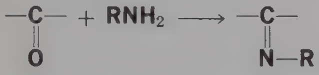
of ammonia.[44a] Similar compounds may be prepared from aldehydes of the form R_2CHCHO and R_3CCHO.[45] Acetaldehyde and α,β-unsaturated aldehydes give alkylpyridine derivatives.[45a] For example, 5-ethyl-2-picoline (**21**) can be obtained from acetaldehyde. Cyclic trimers of **19** may sometimes be isolated as crystalline compounds, but these are unstable in solution.



21

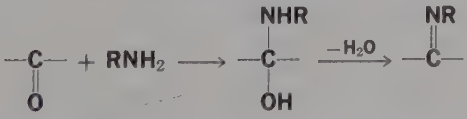
OS **II,** 214, 219; **IV,** 451. Also see OS **III,** 471; **45,** 83.

6-15 The addition of amines to aldehydes and ketones



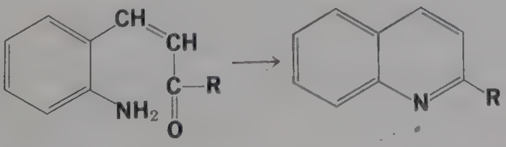
$$\underset{\underset{\text{O}}{\|}}{-\text{C}-} + \text{RNH}_2 \longrightarrow \underset{\underset{\text{N—R}}{\|}}{-\text{C}-}$$

Primary, secondary, and tertiary amines can add to aldehydes and ketones to give different kinds of products. Primary amines give imines. In contrast to imines in which the nitrogen is attached to a hydrogen (reaction **6-14**), these imines are stable enough for isolation. However, they rapidly decompose unless there is at least one aryl group on the nitrogen or the carbon. When there is an aryl group, the compounds are quite stable. They are usually called *Schiff bases,* and this reaction is the best way to prepare them. The reaction is straightforward and proceeds in high yields. The initial N-substituted hemiaminals lose water to give the stable Schiff bases:



$$\underset{\underset{\text{O}}{\|}}{-\text{C}-} + \text{RNH}_2 \longrightarrow -\overset{\overset{\text{NHR}}{|}}{\underset{\underset{\text{OH}}{|}}{\text{C}}}- \xrightarrow{-\text{H}_2\text{O}} -\overset{\overset{\text{NR}}{\|}}{\text{C}}-$$

The reaction is often used to effect ring closure. The *Friedlander quinoline synthesis* is an example:



When secondary amines are added to aldehydes or ketones, the initially formed N,N-disubstituted hemiaminals (**22**) cannot lose water in the same way, and it is possible to isolate them.[46] However, they are usually unstable, and a more stable product is the *aminal* (**23**). Although **22** cannot lose

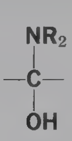
---

[44a] Ogata, Kawasaki, and Okumura, *J. Org. Chem.* **29,** 1985 (1964).

[45] Hasek, Elam, and Martin, *J. Org. Chem.* **26,** 1822 (1961).

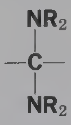
[45a] For a review, see Gelas, *Bull. Soc. chim. France* **1967,** 3093–3101.

[46] For example, see Duhamel and Cantacuzène, *Bull. Soc. chim. France* **1962,** 1843.



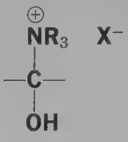
$$NR_2\text{—}\overset{|}{\underset{|}{C}}\text{—}OH$$

22



$$NR_2\text{—}\overset{|}{\underset{|}{C}}\text{—}NR_2$$

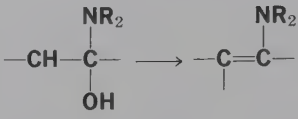
23



$$\overset{\oplus}{N}R_3\text{—}\overset{|}{\underset{|}{C}}\text{—}OH \quad X^-$$

24

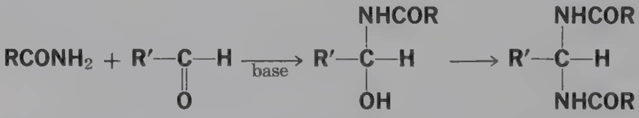
water to give a carbon-nitrogen double bond, if there is an α hydrogen, then water can be lost in that direction to give a carbon-carbon double bond, and the product is an enamine:[47]



$$\text{—CH—}\overset{NR_2}{\underset{OH}{C}}\text{—} \longrightarrow \text{—}\underset{|}{C}\text{=}\overset{NR_2}{C}\text{—}$$

This is the most common method for the preparation of enamines, and usually takes place when an aldehyde or ketone containing an α hydrogen is treated with a secondary amine. The water is usually removed azeotropically. Secondary amine perchlorates react with aldehydes and ketones to give iminium salts (**7**, p. 658).[48] Tertiary amines can only give salts (**24**).

Amides can add to aldehydes in the presence of bases (so the nucleophile is actually RCONH⁻) or acids to give acylated amino alcohols, which often react further to give alkylidene or arylidene bisamides:[49]

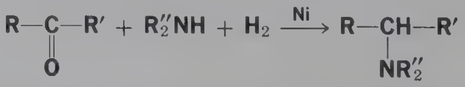


$$RCONH_2 + R'\text{—}\underset{\underset{O}{\|}}{C}\text{—}H \xrightarrow[\text{base}]{} R'\text{—}\overset{NHCOR}{\underset{OH}{C}}\text{—}H \longrightarrow R'\text{—}\overset{NHCOR}{\underset{NHCOR}{C}}\text{—}H$$

If the R′ group contains an α hydrogen, water may split out.

OS **I,** 80, 355, 381; **II,** 31, 49, 65, 202, 231, 422; **III,** 95, 328, 329, 332, 358, 374, 513, 753, 827; **IV,** 210, 605, 638, 824; **40,** 99; **41,** 65; **43,** 34, 40, 49, 68; **44,** 72, 75. Also see OS **IV,** 283, 464.

6-16 Reductive alkylation of ammonia or amines



$$R\text{—}\underset{\underset{O}{\|}}{C}\text{—}R' + R''_2NH + H_2 \xrightarrow{\text{Ni}} R\text{—}\underset{NR''_2}{\underset{|}{CH}}\text{—}R'$$

When an aldehyde or a ketone is treated with ammonia or a primary or secondary amine in the presence of hydrogen and a hydrogenation catalyst, *reductive alkylation* takes place.[50] The reaction may formally be regarded as occurring in the following manner (shown for a primary amine), which probably *does* correspond to the actual sequence of steps:[51]

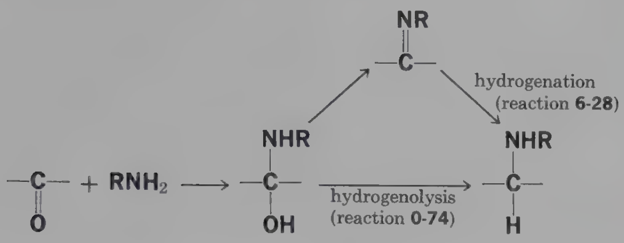
---

[47] For a review, see Szmuszkovicz, *Advan. Org. Chem.* **4,** 1–113 (1963), pp. 9–12.

[48] Leonard and Paukstelis, *J. Org. Chem.* **28,** 3021 (1963).

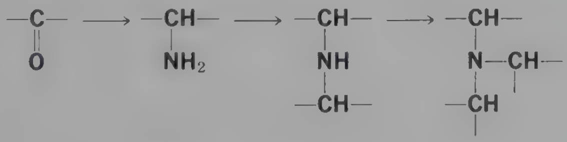
[49] For a review, see Zaugg and Martin, *Org. Reactions* **14,** 52–269 (1965), pp. 91–95, 104–112.

[50] For a review, see Emerson, *Org. Reactions* **4,** 174–255 (1948).



For ammonia and primary amines there are thus two possible pathways, but when secondary amines are involved, only the hydrogenolysis pathway is possible. Other reducing agents may be used instead of hydrogen and a catalyst, among them zinc and HCl, sodium borohydride,[52] and formic acid. When the latter is used, the process is called the *Wallach reaction.* In the particular case where primary or secondary amines are reductively alkylated with *formaldehyde* and formic acid, the method is called the *Eschweiler-Clarke procedure.* It is possible to use ammonium (or amine) salts of formic acid, or formamides, as a substitute for the Wallach conditions. This method is called the *Leuckart reaction,*[53] and in this case the products obtained are often the N-formyl derivatives of the amines, instead of the free amines.

When the reagent is ammonia, it is possible for the initial product to react again, and for this product to react again, so that secondary and tertiary amines are usually obtained as side products:



Similarly, primary amines give tertiary as well as secondary amines. In order to minimize this, the aldehyde or ketone is treated with an excess of ammonia or primary amine (unless of course the higher amine is desired).

Primary amines have been prepared from many aldehydes with at least five carbons and from many ketones by treatment with ammonia and a reducing agent. Smaller aldehydes are usually too reactive to permit isolation of the primary amine. Secondary amines have been prepared by both of the possible procedures: two moles of ammonia and one of aldehyde or ketone, and one mole of primary amine and one of carbonyl compound, the latter method being better for all but aromatic aldehydes. Tertiary amines can be prepared in three ways, but the method is seldom carried out with three moles of ammonia and one of carbonyl compound. Much more often they are prepared from primary or secondary amines.[54] The most common method for this purpose is the Eschweiler-Clarke procedure: treatment of the primary or secondary amine with formaldehyde and formic acid. Amines of the form $RNMe_2$ and R_2NMe are prepared in this manner.

---

[51] See, for example, Le Bris, Lefebvre, and Coussemant, *Bull. Soc. chim. France* **1964**, 1366, 1374, 1584, 1594.

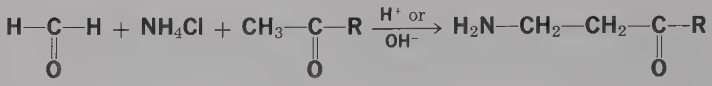
[52] Schellenberg, *J. Org. Chem.* **28**, 3259 (1963).

[53] For a review, see Moore, *Org. Reactions* **5**, 301–330 (1949); for a discussion of the mechanism, see Lukasiewicz, *Tetrahedron* **19**, 1789 (1963).

Reductive alkylation has also been carried out on nitro, nitroso, azo, and other compounds which are reduced *in situ* to primary or secondary amines.

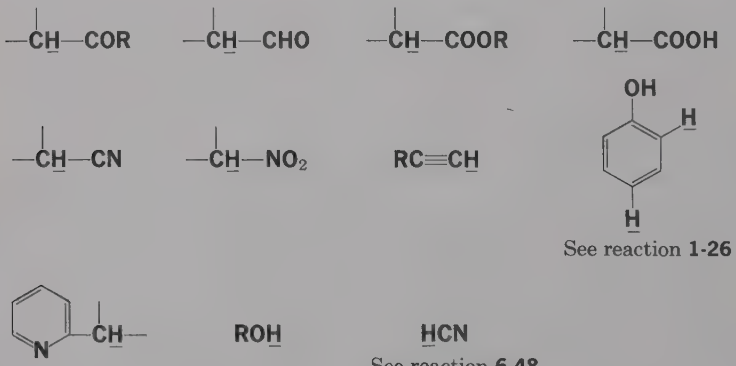
OS **I,** 347, 528, 531; **II,** 503; **III,** 328, 501, 717, 723; **IV,** 603.

6-17 The Mannich reaction



$$H-\underset{\underset{O}{\|}}{C}-H + NH_4Cl + CH_3-\underset{\underset{O}{\|}}{C}-R \xrightarrow[OH^-]{H^+\text{ or}} H_2N-CH_2-CH_2-\underset{\underset{O}{\|}}{C}-R$$

In the *Mannich reaction,* formaldehyde (or sometimes another aldehyde) is condensed with ammonia, in the form of its salt, and a compound containing an active hydrogen.[55] This may formally be considered as an addition of ammonia to give H_2NCH_2OH, followed by a nucleophilic substitution (see the discussion of the mechanism on p. 672). Instead of ammonia, the reaction may be carried out with salts of primary or secondary amines, or with amides,[56] in which cases the product is substituted on the nitrogen with R, R_2, and RCO, respectively. Arylamines do not normally give the reaction. In any case, the product is referred to as a *Mannich base.* Many active hydrogen compounds give the reaction. Among these are the following types, with the active hydrogen underlined:



See reaction **1-26**

See reaction **6-48**

---

[54] For a review of the preparation of tertiary amines by reductive alkylation, see Spialter and Pappalardo, "The Acyclic Aliphatic Tertiary Amines," pp. 44–52, The Macmillan Company, New York, 1965.

[55] For reviews, see Blicke, *Org. Reactions* **1,** 303–341 (1942); House, "Modern Synthetic Reactions," pp. 230–234, W. A. Benjamin, Inc., New York, 1965.

[56] See Hellmann, in Foerst, "Newer Methods of Preparative Organic Chemistry," vol. 2, pp. 277–302, Academic Press Inc., New York, 1963. [This article also appeared in *Angew. Chem.* **69,** 463 (1957).]

The Mannich base may react further, in three ways. If it is a primary or secondary amine, then it may condense with one or two additional molecules of aldehyde and active compound, e.g.,

$$H_2NCH_2CH_2COR \xrightarrow[CH_3COR]{HCHO} HN(CH_2CH_2COR)_2 \xrightarrow[CH_3COR]{HCHO} N(CH_2CH_2COR)_3$$

If the active hydrogen compound has two or three active hydrogens, the Mannich base may condense with one or two additional molecules of aldehyde and ammonia or amine, e.g.,

$$H_2NCH_2CH_2COR \xrightarrow[NH_3]{HCHO} (H_2NCH_2)_2CHCOR \xrightarrow[NH_3]{HCHO} (H_2NCH_2)_3CCOR$$

Another further reaction consists of condensation of the Mannich base with excess formaldehyde:

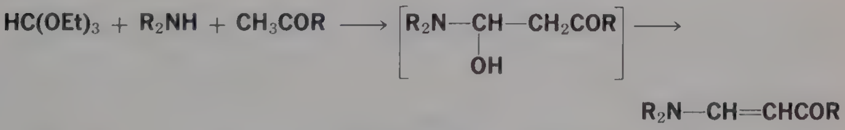
$$H_2NCH_2CH_2COR + HCHO \longrightarrow H_2C{=}NCH_2CH_2COR$$

Sometimes it is possible to obtain these products of further condensation as the main products of the reaction. At other times they are side products.

When the Mannich base contains an amino group β to a carbonyl (and it usually does), then ammonia is easily eliminated, and this is a route to α,β-unsaturated aldehydes, ketones, esters, etc.:

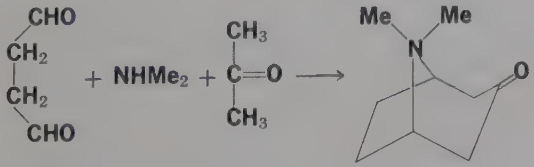
$$H_2NCH_2CH_2COR \xrightarrow[\Delta]{} H_2C{=}CHCOR$$

Enamines may be prepared by a Mannich reaction involving a secondary amine and formic acid (in the form of ethyl orthoformate) instead of formaldehyde, e.g.,



$$HC(OEt)_3 + R_2NH + CH_3COR \longrightarrow \left[R_2N{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_2COR \right] \longrightarrow R_2N{-}CH{=}CHCOR$$

The Mannich reaction is an important biosynthetic route to natural products, mainly alkaloids, and some of these routes have been duplicated in the laboratory. A classic example may be found in the synthesis of tropinone by Robinson in 1917. Atropine, a natural product, is an ester of tropic acid ($PhCH(COOH)CH_2OH$) and tropine. Tropine is a secondary alcohol which may be oxidized to the corresponding ketone, tropinone (**25**). Robinson synthesized tropinone by a Mannich reaction involving succindialdehyde, dimethylamine, and acetone:[57]



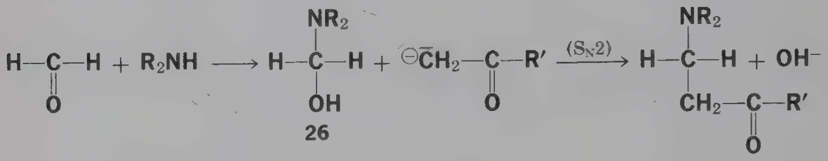
25

---

[57] Robinson, *J. Chem. Soc.* **111**, 762 (1917).

Over the years there has been much controversy about the mechanism of the Mannich reaction, especially as to whether the aldehyde is first attacked by the active hydrogen compound (as in reaction **6-39**) or by the ammonia or amine (as in reaction **6-15**). The evidence seems to favor the latter course. Studies of the reaction kinetics have led to the following mechanistic proposals:[58]

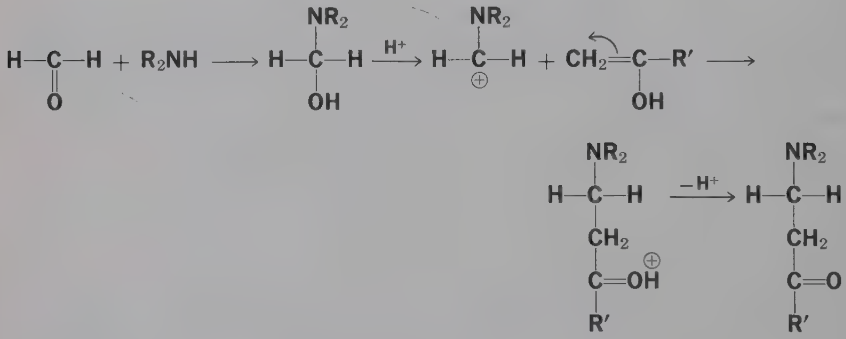
The base-catalyzed reaction



$$H{-}\underset{\substack{\Vert\\ O}}{C}{-}H + R_2NH \longrightarrow \underset{\mathbf{26}}{H{-}\overset{\substack{NR_2\\ |}}{\underset{\substack{|\\ OH}}{C}}{-}H} + {}^{\ominus}\bar{C}H_2{-}\underset{\substack{\Vert\\ O}}{C}{-}R' \xrightarrow{(S_N2)} H{-}\overset{\substack{NR_2\\ |}}{\underset{\substack{|\\ CH_2{-}\underset{\substack{\Vert\\ O}}{C}{-}R'}}{C}}{-}H + OH^-$$

There is evidence that in basic media the intermediate which undergoes the nucleophilic substitution may be $H_2C(NR_2)_2$ (**27**) instead of **26**,[59] but it has been shown that **26** are more reactive than **27** in this type of step.[60]

The acid-catalyzed reaction



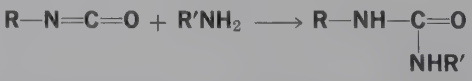
$$H{-}\underset{\substack{\Vert\\ O}}{C}{-}H + R_2NH \longrightarrow H{-}\overset{\substack{NR_2\\ |}}{\underset{\substack{|\\ OH}}{C}}{-}H \xrightarrow{H^+} H{-}\overset{\substack{NR_2\\ |}}{\underset{\oplus}{C}}{-}H + CH_2{=}\underset{\substack{|\\ OH}}{C}{-}R' \longrightarrow$$

$$H{-}\overset{\substack{NR_2\\ |}}{\underset{\substack{|\\ CH_2\\ |\\ C{=}\overset{\oplus}{O}H\\ |\\ R'}}{C}}{-}H \xrightarrow{-H^+} H{-}\overset{\substack{NR_2\\ |}}{\underset{\substack{|\\ CH_2\\ |\\ C{=}O\\ |\\ R'}}{C}}{-}H$$

According to this mechanism, it is the free amine and not the salt which reacts, even in acid solution; and the active-hydrogen compound (in the acid-catalyzed process) reacts as the enol, when that is possible. This latter step is similar to that in reaction **2-4** (p. 458).

OS **III,** 305; **IV,** 281, 515, 816. Also see reactions **6-48** and **1-26.**

6-18 The addition of amines to isocyanates



$$R{-}N{=}C{=}O + R'NH_2 \longrightarrow R{-}NH{-}\underset{\substack{|\\ NHR'}}{C}{=}O$$

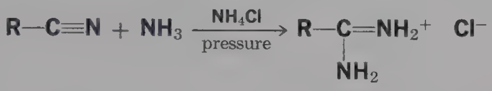
---

[58] Cummings and Shelton, *J. Org. Chem.* **25,** 419 (1960).
[59] Burckhalter, Wells, and Mayer, *Tetrahedron Letters* **1964,** 1353.
[60] Fernandez, *Tetrahedron Letters* **1964,** 2889.

Primary and secondary amines may be added to isocyanates to give substituted ureas. Isothiocyanates give thioureas. This is an excellent method for the preparation of ureas and thioureas, and these compounds are often used as derivatives for primary and secondary amines. Cyanic acid (HNCO) also gives the reaction; usually its salts (for example, NaNCO) are used. Wöhler's famous synthesis of urea involved the addition of ammonia to a salt of cyanic acid.

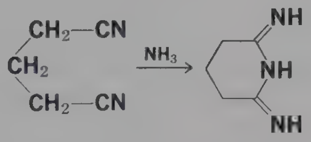
OS **II,** 79; **III,** 76, 617, 735; **IV,** 49, 180, 213, 515, 700; **42,** 87; **45,** 69, 70.

6-19 The addition of ammonia or amines to nitriles



$$R{-}C{\equiv}N + NH_3 \xrightarrow[\text{pressure}]{NH_4Cl} R{-}\underset{\displaystyle NH_2}{\underset{|}{C}}{=}NH_2^+ \quad Cl^-$$

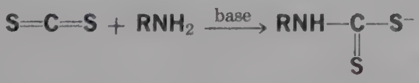
Unsubstituted amidines (in the form of their salts) may be prepared by addition of ammonia to nitriles. Many amidines have been made in this way.[61] Dinitriles of suitable chain length may give imidines:[62]



Primary and secondary amines may be used instead of ammonia, to give substituted amidines, but only if the nitrile contains electron-withdrawing groups; for example, Cl_3CCN gives the reaction. Ordinary nitriles do not react, and, in fact, acetonitrile is often used as a solvent in this reaction.[63] However, aniline may be added to benzonitrile with $AlCl_3$ as catalyst.

OS **I,** 302 [but also see OS **43,** 48]; **IV,** 245, 247, 515, 566, 769.

6-20 The addition of amines to carbon disulfide



$$S{=}C{=}S + RNH_2 \xrightarrow{\text{base}} RNH{-}\underset{\displaystyle S}{\underset{\|}{C}}{-}S^-$$

Salts of dithiocarbamic acid may be prepared by the addition of primary amines to carbon disulfide. This reaction is similar to reaction **6-11.** H_2S may be eliminated from the product, directly, or indirectly, to give isothiocyanates, RNCS.

OS **I,** 447; **III,** 360, 394, 599, 763; **45,** 19.

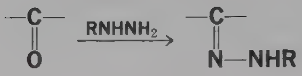
[61] See, for example, Schaefer and Krapcho, *J. Org. Chem.* **27,** 1255 (1962).

[62] Elvidge, Linstead, and Salaman, *J. Chem. Soc.* **1959,** 208.

[63] Grivas and Taurins, *Can. J. Chem.* **39,** 761 (1961).

E. Other nitrogen nucleophiles

6-21 The addition of hydrazine derivatives to carbonyl compounds



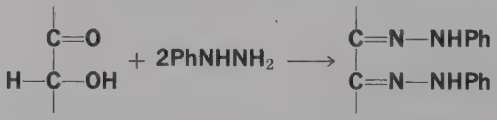
$$-\underset{\underset{\text{O}}{\|}}{\text{C}}- \xrightarrow{\text{RNHNH}_2} -\underset{\underset{\text{N—NHR}}{\|}}{\text{C}}-$$

The product of condensation of a hydrazine and an aldehyde or ketone is called a hydrazone. Hydrazine itself gives hydrazones only with aryl ketones. With other aldehydes and ketones, either no useful product can be isolated, or the remaining NH_2 group condenses with a second mole of carbonyl compound to give an *azine.* This type of product is especially important for aromatic aldehydes:

$$ArCH{=}N{-}NH_2 + ArCHO \longrightarrow ArCH{=}N{-}N{=}CHAr$$

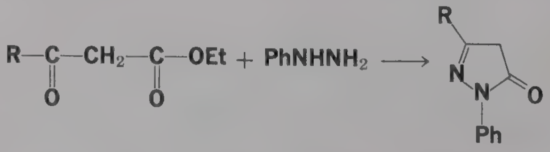
An azine

Arylhydrazines, especially phenyl, *p*-nitrophenyl, and 2,4-dinitrophenyl, are used much more often, and give the corresponding hydrazones with most aldehydes and ketones. Since these are usually solids, they make excellent derivatives and are commonly employed for this purpose. α-Hydroxy aldehydes and ketones and α-dicarbonyl compounds give *osazones,* in which two adjacent carbons have carbon-nitrogen double bonds:



An osazone

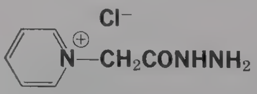
In contrast to this behavior, β-diketones and β-keto esters give *pyrazoles* and *pyrazolones,* respectively (illustrated for β-keto esters):



Other hydrazine derivatives frequently used to prepare the corresponding hydrazone are semicarbazide ($NH_2NHCONH_2$) (in which case the hydrazone is called a semicarbazone) and *Girard's reagents T and P,* in which case the hydrazone is water-soluble because of the ionic group. Girard's reagents are often used for purification of carbonyl compounds.

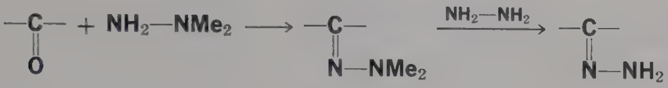
$$Cl^- \quad Me_3\overset{\oplus}{N}CH_2CONHNH_2$$

Girard's reagent T



Girard's reagent P

Simple N-unsubstituted hydrazones may be obtained by an exchange reaction. The N,N-dimethylhydrazone is prepared first and then treated with hydrazine:[64]

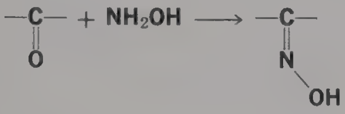


$$-\underset{\underset{O}{\|}}{C}- + NH_2{-}NMe_2 \longrightarrow -\underset{\underset{N-NMe_2}{\|}}{C}- \xrightarrow{NH_2-NH_2} -\underset{\underset{N-NH_2}{\|}}{C}-$$

No azines are formed under these conditions.

OS **II,** 395; **III,** 96, 351; **IV,** 351, 377, 536, 884; **45,** 1. Also see OS **III,** 708.

6-22 The formation of oximes

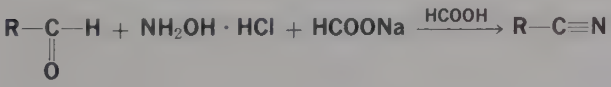


$$-\underset{\underset{O}{\|}}{C}- + NH_2OH \longrightarrow -\underset{\underset{\underset{\diagdown OH}{N}}{\|}}{C}-$$

In a reaction very much like **6-21,** oximes may be prepared by the addition of hydroxylamine to aldehydes or ketones. Derivatives of hydroxylamine, for example, H_2NOSO_3H and $HON(SO_3Na)_2$, have also been used. For hindered ketones, such as hexamethylacetone, high pressures (e.g., 10,000 atm) may be necessary.[65] Another procedure, successful for hindered ketones, is to allow the ketone to stand with hydroxylamine and a strongly basic catalyst for 1 to 6 months. High yields of oximes are achieved in this way by those who have the patience to wait. Reactions which proceed over a long time but cannot be rushed by increase in temperature have been called "lethargic reactions."[66]

OS **I,** 318, 327; **II,** 70, 204, 313, 622; **III,** 690; **IV,** 229; **46,** 13.

6-23 The conversion of aldehydes to nitriles



$$R-\underset{\underset{O}{\|}}{C}-H + NH_2OH\cdot HCl + HCOONa \xrightarrow{HCOOH} R-C\equiv N$$

Aldehydes may be converted to nitriles in one step by refluxing with hydroxylamine hydrochloride and sodium formate in formic acid or sodium acetate in acetic acid.[67] The reaction is a combination of reactions **6-22** and **7-30** (p. 776). Direct nitrile formation has also been accomplished with certain derivatives of NH_2OH, notably $F_3CCONHOCOCF_3$.[68] Another method involves treatment with hydrazoic acid, though the Schmidt reaction (**8-18**, p. 819) may compete. A possible rationalization is the following:

---

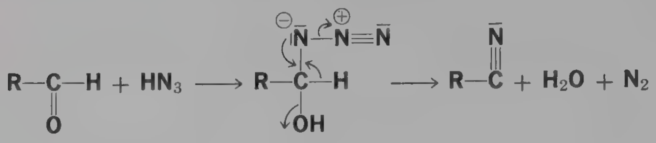
[64] Newkome and Fishel, *J. Org. Chem.* **31,** 677 (1966).

[65] Jones, Tristram, and Benning, *J. Am. Chem. Soc.* **81,** 2151 (1959).

[66] Pearson and Keaton, *J. Org. Chem.* **28,** 1557 (1963).

[67] Hunt, *Chem. Ind. (London)* **1961,** 1873; van Es, *J. Chem. Soc.* **1965,** 1564.

[68] Pomeroy and Craig, *J. Am. Chem. Soc.* **81,** 6340 (1959).



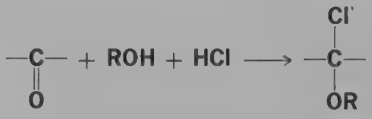
Aromatic aldehydes have been converted to nitriles in good yield with $NH_4H_2PO_4$ and nitropropane in acetic acid,[69] and with ammonia and iodine or lead tetraacetate.[70] Also see reaction **9-5** (p. 866).

OS **43,** 58.

6-24 The addition of nitriles to aldehydes is discussed at reaction **6-58.**

F. Halogen nucleophiles

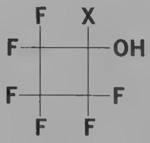
6-25 The formation of α-halo ethers



$$-\underset{\underset{O}{\|}}{C}- + ROH + HCl \longrightarrow -\overset{\overset{Cl}{|}}{\underset{\underset{OR}{|}}{C}}-$$

α-Halo ethers may be prepared by treatment of aldehydes and ketones with an alcohol and HX, though α-halo ethers from simple aldehydes such as formaldehyde are unstable and the reaction tends to reverse. The reaction is applicable to aliphatic aldehydes and ketones and to primary and secondary alcohols. Aromatic aldehydes and ketones react poorly.[71]

The addition of HX to an aldehyde or ketone gives α-halo alcohols, which are usually unstable, though exceptions are known, especially with perfluoro and perchloro species. For example, **28** (X = any of the four halogens) were



28

prepared in this way.[72] Unstable α-halo alcohols may be quite stable in the dimeric form $2XCR_2OH \longrightarrow XCR_2OCR_2X$.

OS **I,** 377; **IV,** 101, 748.

---

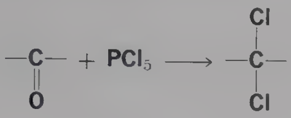
[69] Blattner, Lukaszewski, and de Stevens, *J. Am. Chem. Soc.* **83,** 2203 (1961).

[70] Misono, Osa, and Koda, *Bull. Chem. Soc. Japan* **39,** 854 (1966); Parameswaran and Friedman, *Chem. Ind.* (*London*) **1965,** 988.

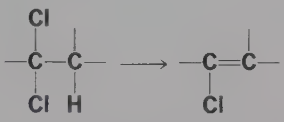
[71] Klages and Mühlbauer, *Chem. Ber.* **92,** 1818 (1959).

[72] Andreades and England, *J. Am. Chem. Soc.* **83,** 4670 (1961).

6-26 The formation of *gem*-dihalides from aldehydes and ketones

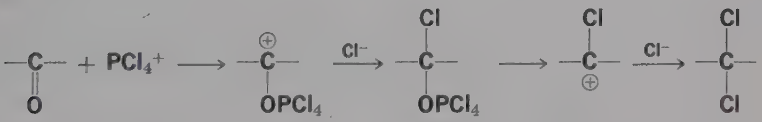


Aliphatic aldehydes and ketones may be converted to *gem*-dichlorides by treatment with PCl_5. The reaction fails for perhalo ketones.[73] If the aldehyde or ketone has an α hydrogen, then elimination of HCl may follow, and a vinyl chloride is a frequent side product:[74]



These compounds may even become the main products.[75]

The mechanism of *gem*-dichloride formation involves initial attack of PCl_4^+ (which is present in solid PCl_5) at the oxygen, followed by addition of Cl^- to the carbon:[76]



This chloride ion may come from PCl_6^- (which is also present in solid PCl_5). There follows a two-step S_N1 process. Alternatively, **29** may be converted to **31** without going through **30**, by an S_Ni process.

This reaction has sometimes been performed on esters, though these compounds very seldom undergo any addition to the C═O bond. An example is the conversion of $F_3CCOOPh$ to F_3CCCl_2OPh.[77] However, formates commonly give the reaction. PBr_5 does not give good yields of *gem*-dibromides.

Many aldehydes and ketones have been converted to *gem*-difluoro compounds with SF_4,[78] including quinones, which give 1,1,4,4-tetrafluorocyclohexadiene derivatives. Carboxylic acids, acyl chlorides, and amides react with SF_4 to give 1,1,1-trifluorides. In these cases the first product is the acyl fluoride, which then undergoes the *gem*-difluorination reaction:

---

[73] Farah and Gilbert, *J. Org. Chem.* **30**, 1241 (1965).

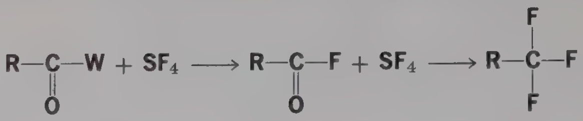
[74] For example, see Nikolenko and Popov, *J. Gen. Chem. USSR* **32**, 29 (1962).

[75] See, for example, Newman, Fraenkel, and Kirn, *J. Org. Chem.* **28**, 1851 (1963).

[76] Newman and Wood, *J. Am. Chem. Soc.* **81**, 4300 (1959).

[77] Kirsanov and Molosnova, *J. Gen. Chem. USSR* **28**, 31 (1958); Clark and Simons, *J. Org. Chem.* **26**, 5197 (1961).

[78] For a review, see Smith, *Angew. Chem. Intern. Ed. Engl.* **1**, 467–475 (1962). Also see Hasek, Smith, and Engelhardt, *J. Am. Chem. Soc.* **82**, 543 (1960).



$$R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}W + SF_4 \longrightarrow R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}F + SF_4 \longrightarrow R{-}\overset{\displaystyle F}{\overset{|}{\underset{\displaystyle F}{\underset{|}{C}}}}{-}F$$

$W = OH, Cl, NH_2, NHR$

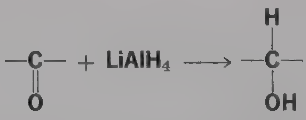
The acyl fluoride can be isolated. Esters also give trifluorides, though more vigorous conditions are required, but in this case the carbonyl group of the ester is attacked first, and RCF_2OR' can be isolated from $RCOOR'$ and then converted to the trifluoride. Anhydrides can react in either manner, and both types of intermediate are isolable under the right conditions. SF_4 even converts carbon dioxide to CF_4. Another reagent which gives *gem*-difluorination is SOF_2.[79]

The mechanism with SF_4 is probably similar in general nature, if not in specific detail, to that with PCl_5.

OS **II,** 549; **41,** 104; **44,** 39. Also see OS **I,** 506.

G. Attack by hydrogen

6-27 Reduction of aldehydes and ketones to alcohols



$$-\underset{\displaystyle O}{\underset{\|}{C}}- + LiAlH_4 \longrightarrow -\overset{\displaystyle H}{\overset{|}{\underset{\displaystyle OH}{\underset{|}{C}}}}-$$

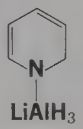
Aldehydes may be reduced to primary alcohols, and ketones to secondary alcohols, by a number of reducing agents, of which lithium aluminum hydride and other metallic hydrides are the most commonly used.[80] These reagents have two main advantages over most of the reagents which were used before the discovery of $LiAlH_4$: they do not reduce carbon-carbon double (or triple) bonds, and they generally contain a lot of hydrogen in a small amount of reagent—with $LiAlH_4$, all four hydrogens are usable for reduction. The reaction is broad and general. $LiAlH_4$ easily reduces aliphatic, aromatic, alicyclic, and heterocyclic aldehydes, containing double or triple bonds and/or nonreducible groups such as NR_3, OH, OR, F, etc. If the molecule contains a group reducible by $LiAlH_4$ (for example, NO_2, CN, COOR, etc.), then it is reduced also. $NaBH_4$ has a similar scope but is more selective and so may be used with NO_2, Cl, etc., in the molecule. Another advantage of $NaBH_4$

---

[79] Fawcett, Tullock, and Coffman, *J. Am. Chem. Soc.* **84**, 4275 (1962).

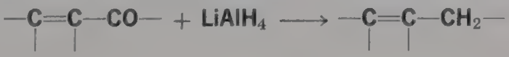
[80] A treatise on reduction with metal hydrides is by Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, 1956. Review articles on specific aspects of this subject are: Brown, *Org. Reactions* **6**, 469–509 (1951); Schenker, *Angew. Chem.* **73**, 81–106 (1961); Brown, *J. Chem. Ed.* **38**, 173–179 (1961); and Hörmann, in Foerst, "Newer Methods of Preparative Organic Chemistry," vol. 2, pp. 213–226, Academic Press Inc., New York, 1963. [This article also appeared in *Angew. Chem.* **68**, 601 (1956).]

is that it may be used in water and so reduces compounds such as sugars that are not soluble in organic solvents. The double bonds present in the molecule may be isolated, conjugated, or even conjugated with the C=O group, although in the latter case they are sometimes affected. For example, cinnamaldehyde with $LiAlH_4$ gives reduction of both double bonds, so that the product is $PhCH_2CH_2CH_2OH$, while $NaBH_4$ reduces only the C=O, so that the product is $PhCH{=}CHCH_2OH$. The scope of these reagents with ketones is similar to that with aldehydes. $LiAlH_4$ reduces even sterically hindered ketones. With suitable hydrides a degree of selectivity is possible: $NaBH_4$ in isopropyl alcohol reduces aldehydes much faster than ketones,[81] and lithium N-dihydropyridylaluminum hydride (**32**) reduces diaryl ketones



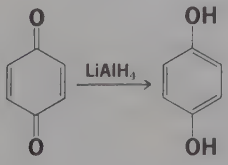
32

much better than it does dialkyl or alkyl aryl ketones.[82] Most other hydrides reduce diaryl ketones more slowly than other types of ketones. It is obvious that reagents can often be found to reduce one kind of carbonyl function in the presence of another. Aldehydes and ketones may often be reduced in the presence of other reducible groups, if a suitable reagent is used. For a discussion of selectivity in reduction reactions, see page 890. α,β-Unsaturated ketones are usually reduced to *olefins* with $LiAlH_4$:[83]



$$-\underset{|}{C}=\underset{|}{C}-CO- + LiAlH_4 \longrightarrow -\underset{|}{C}=\underset{|}{C}-CH_2-$$

(see reaction **9-34**, p. 891). Certain ketones are cleaved by treatment with $LiAlH_4$ in pyridine; for example, $Ph_3CCOPh \longrightarrow Ph_3CH + PhCH_2OH$.[84] Quinones are reduced with $LiAlH_4$ to the corresponding hydroquinones:



$LiAlH_4$ reduces ketenes to alcohols: $Ph_2C{=}C{=}O \longrightarrow PhCH_2CH_2OH$.[85]

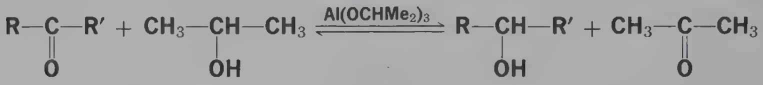
[81] Brown, Wheeler, and Ichikawa, *Tetrahedron* **1**, 214 (1957).
[82] Lansbury and Peterson, *J. Am. Chem. Soc.* **84**, 1756 (1962).
[83] Broome, Brown, Roberts, and White, *J. Chem. Soc.* **1960**, 1406.
[84] Lansbury, *Chem. Ind.* (*London*) **1960**, 151.
[85] Mićović, Rogić, and Mihailović, *Tetrahedron* **1**, 340 (1957).

Among other reagents which reduce aldehydes and ketones to alcohols are the following:

1. *Hydrogen and a catalyst.* The most common catalysts are platinum, copper chromite, and ruthenium. Before the discovery of the metal hydrides this was one of the most common ways of effecting this reduction, but it suffers from the fact that C=C, C≡C, C=N, and C≡N bonds are more susceptible to attack than are C=O bonds.

2. *Sodium ethoxide in ethanol.* This is called the *Bouveault-Blanc procedure* and was more popular for the reduction of esters (reaction **9-39**, p. 896) than of aldehydes or ketones before the discovery of $LiAlH_4$.

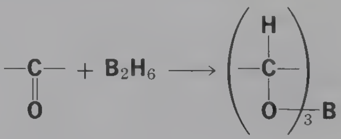
3. *Isopropyl alcohol and aluminum isopropoxide.* This is called the *Meerwein-Ponndorf-Verley reduction.*[86] It is reversible, and the reverse reaction is known as the *Oppenauer oxidation* (reaction **9-3**, p. 862):



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}R' + CH_3{-}\underset{\underset{OH}{|}}{CH}{-}CH_3 \xrightleftharpoons{Al(OCHMe_2)_3} R{-}\underset{\underset{OH}{|}}{CH}{-}R' + CH_3{-}\underset{\underset{O}{\|}}{C}{-}CH_3}$$

The equilibrium is shifted by removal of the acetone by distillation. The reaction takes place under very mild conditions and is highly specific for aldehydes and ketones, so that many functional groups may be present without themselves being reduced. This includes acetals, so that one of two carbonyl groups in a molecule may be specifically reduced by conversion of the other to an acetal. β-Keto esters, β-diketones, and other ketones and aldehydes with a relatively high enol content do not give this reaction.

4. *Diborane* (B_2H_6) reduces aldehydes and ketones in a manner similar to its addition to C=C bonds (reaction **5-13**, p. 599). That is, the boron adds to the oxygen and the hydrogen to the carbon:[87]



$$\mathrm{{-}\underset{\underset{O}{\|}}{C}{-} + B_2H_6 \longrightarrow \left(\begin{array}{c} H \\ | \\ {-}C{-} \\ | \\ O \end{array}\right)_3 B}$$

The borate is then hydrolyzed to the alcohol.

5. *Diimide* (N_2H_2, see p. 596) reduces aromatic aldehydes and ketones, but aliphatic carbonyl compounds react very poorly.[88]

6. In the Cannizzaro reaction (**9-62**, p. 908) aldehydes without an α hydrogen are reduced to alcohols.

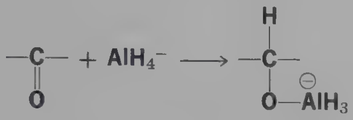
With most reagents there is an initial attack on the carbon of the carbonyl group by H or some carrier of it, though with B_2H_6 the initial attack is on the oxygen. Detailed mechanisms are not known in most cases. With metallic hydrides of aluminum or boron, the attacking species is the AlH_4^- (or BH_4^-) ion, which, in effect, transfers H^- to the carbon.[89] The freed AlH_3 then complexes with the oxygen from the same molecule, or from a different one:

---

[86] For a review, see Wilds, *Org. Reactions* **2**, 178–223 (1944).

[87] Brown and Subba Rao, *J. Am. Chem. Soc.* **82**, 681 (1960); Brown and Korytnyk, *J. Am. Chem. Soc.* **82**, 3866 (1960). Also see Brown, "Hydroboration," pp. 247–250, W. A. Benjamin, Inc., New York, 1962.

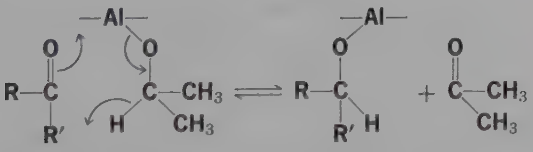
[88] van Tamelen, Davis, and Deem, *Chem. Commun.* **1965**, 71.



33

The complex must now be hydrolyzed to the alcohol. If the reaction is performed in a protic solvent, then AlH_3 coordinates with the solvent instead, and a proton from the solvent goes to the oxygen. Free H^- cannot be the attacking entity in most reductions with boron or aluminum hydrides, because the reactions are frequently sensitive to the size of the MH_4^- [or $MR_mH_n^-$ or $M(OR)_mH_n^-$, etc.]. It has been shown that $NaBH_4$ *molecules* are not the attacking species either, since they react only in solvents in which they are ionized to Na^+ and BH_4^-.[90] There has been much controversy about whether the initial complex (**33**) can reduce another carbonyl to give $(\text{H—}\overset{|}{\underset{|}{\text{C}}}\text{—O})_2\text{AlH}_2$, and so on. It has been shown[91] that this is probably not the case but that, more likely, **33** disproportionates to $(\text{H—}\overset{|}{\underset{|}{\text{C}}}\text{—O})_4\text{Al}$ and AlH_4 , which is the only attacking species. The use of tin hydrides, such as Ph_2SnH_2, gives alcohols from aldehydes or ketones directly; that is, both hydrogens come from the hydride, and no hydrolysis is needed.[92]

The Meerwein-Ponndorf-Verley reaction usually involves a cyclic transition state:

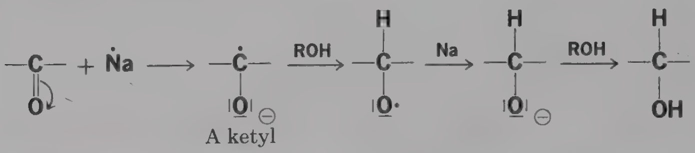


but in some cases two moles of aluminum alkoxide are involved, one attacking the carbon and the other the oxygen, a conclusion which stems from the finding that in these cases the reaction was 1.5 order in alkoxide.[93] It has been shown by deuterium labeling that it is the α hydrogen of the alkoxide which appears at the carbonyl carbon of the starting aldehyde or ketone.[94] Although we have depicted a cyclic mechanism, it is possible to visualize it as occurring in three phases: (1) coordination of the ketone with the alkoxide; (2) hydride transfer; and (3) separation of the new complex. There is controversy over which step is rate-determining: some feel that it is hydride transfer,[95] and others claim that it is none of these, but a subsequent step, in which the alkoxide is hydrolyzed.[96] Although, for simplicity, we have shown the alkoxide as a monomer, it actually exists as trimers and tetramers, and it is these that react.[94]

---

[89] Vail and Wheeler, *J. Org. Chem.* **27**, 3803 (1962).
[90] Brown and Ichikawa, *J. Am. Chem. Soc.* **83**, 4372 (1961).
[91] Haubenstock and Eliel, *J. Am. Chem. Soc.* **84**, 2363 (1962).
[92] Kuivila and Beumel, *J. Am. Chem. Soc.* **83**, 1246 (1961).
[93] Moulton, Van Atta, and Ruch, *J. Org. Chem.* **26**, 290 (1961).
[94] Williams, Krieger, and Day, *J. Am. Chem. Soc.* **75**, 2404 (1953).

In the Meerwein-Ponndorf-Verley reaction, then, the "carrier" of H^- is the α-CH of the alkoxide. This is also the case in reductions involving NaOEt in ethanol, and this was also determined by deuterium labeling.[97] However, when metallic sodium is present in ethanol, *it* can reduce the carbonyl, in an entirely different manner:



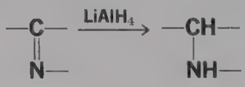
In this reaction *both* hydrogens come from the OH group of the solvent, in sharp contrast to the situation with NaOEt in ethanol, where one hydrogen comes from the OH group, but the other from the α-carbon. The ketyl intermediate can be isolated in those cases in which sodium is present.

The mechanism of catalytic hydrogenation of aldehydes and ketones is probably similar to that of reaction **5-11** (p. 591), though not much is known about it.[98]

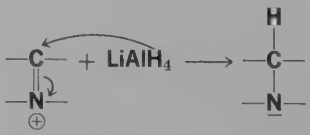
For other reduction reactions of aldehydes and ketones, see reactions **9-34** (p. 891) and **9-57** (p. 903). Also see reaction **9-62** (p. 908).

OS **I,** 90, 304, 554; **II,** 317, 545, 598; **III,** 286; **IV,** 15, 25, 216, 660; **40,** 14; **42,** 66; **45,** 57.

6-28 Reduction of the carbon-nitrogen double bond



Imines, Schiff bases, hydrazones, and other C=N compounds may be reduced with $LiAlH_4$, $NaBH_4$, NaOEt, or hydrogen and a catalyst. Iminium salts are also reduced by $LiAlH_4$, though here there is no "addition" to the nitrogen:



---

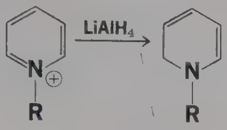
[95] Shiner, Whittaker, and Fernandez, *J. Am. Chem. Soc.* **85,** 2318 (1963); Shiner and Whittaker, *J. Am. Chem. Soc.* **85,** 2337 (1963).

[96] Yager and Hancock, *J. Org. Chem.* **30,** 1174 (1965).

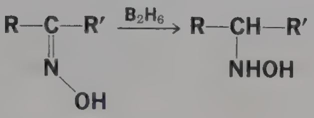
[97] Dar'eva, Miklukhin, and Rekasheva, *J. Gen. Chem. USSR* **29,** 273 (1960).

[98] For example, see Newham and Burwell, *J. Am. Chem. Soc.* **86,** 1179 (1964).

$LiAlH_4$ similarly reduces N-alkylpyridinium salts:



Oximes are generally reduced to amines (reaction **9-45,** p. 899), but simple addition of H_2 to give hydroxylamines can be accomplished with diborane:[99]



$$\text{R}-\underset{\underset{\displaystyle \text{N}-\text{OH}}{\|}}{\text{C}}-\text{R}' \xrightarrow{B_2H_6} \text{R}-\underset{\underset{\displaystyle \text{NHOH}}{|}}{\text{CH}}-\text{R}'$$

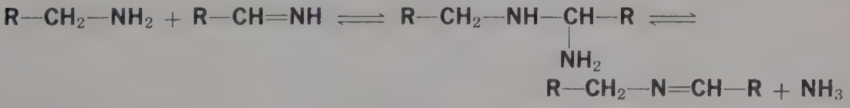
OS **III,** 328, 827. Also see OS **IV,** 283.

6-29 The reduction of nitriles to amines

$$R-C\equiv N + LiAlH_4 \longrightarrow R-CH_2-NH_2$$

Nitriles may be reduced to primary amines with many reducing agents, including $LiAlH_4$, B_2H_6, NaOEt, and hydrogen and a catalyst,[100] though $NaBH_4$ does not give the reaction. The reaction is of wide scope and has been applied to many nitriles. Secondary amines are often side products, arising from the following sequence of steps:

$$R-C\equiv N \longrightarrow R-CH{=}NH \longrightarrow R-CH_2-NH_2$$



$$R-CH_2-NH_2 + R-CH{=}NH \rightleftharpoons R-CH_2-NH-\underset{\underset{\displaystyle NH_2}{|}}{CH}-R \rightleftharpoons R-CH_2-N{=}CH-R + NH_3$$

$$R-CH_2-N{=}CH-R \longrightarrow R-CH_2-NH-CH_2-R$$

These side products may be avoided by adding a compound such as acetic anhydride, which removes the primary amine as soon as it is formed, or by the use of excess ammonia to drive the equilibria backward.

It is not possible to stop with the addition of only one mole of hydrogen, that is, to convert the nitrile to an imine, except where the imine is subsequently hydrolyzed (reaction **6-30**).

OS **III,** 229, 358, 720.

---

[99] Feuer and Vincent, *J. Am. Chem. Soc.* **84,** 3771 (1962); Feuer, Vincent, and Bartlett, *J. Org. Chem.* **30,** 2877 (1965); Ioffe, Tartakovskii, Medvedova, and Novikov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964,** 1446.

[100] See, for example, Freifelder, *J. Am. Chem. Soc.* **82,** 2386 (1960). For a review of the reduction of dinitriles with hydrogen, see Friedlin and Sladkova, *Russ. Chem. Rev.* **33,** 319–330 (1964).

6-30 The reduction of nitriles to aldehydes

$$R{-}C{\equiv}N \xrightarrow[\text{2. hydrolysis}]{\text{1. HCl, SnCl}_2} R{-}CH{=}O$$

There are two principal methods for the reduction of nitriles to aldehydes.[101] In one of these, known as the *Stephen reduction,* the nitrile is treated with HCl to form

$$RCCl{=}NH_2^+ \quad Cl^-$$

34

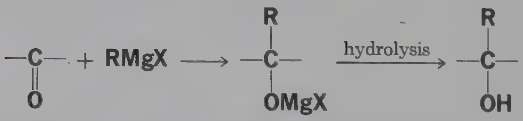
which is reduced with anhydrous $SnCl_2$ to RCH=NH, which precipitates as a complex with $SnCl_4$ and is then hydrolyzed (reaction **6-2**) to the aldehyde. The Stephen reduction is most successful when R is aromatic, but it can be done for aliphatic R up to about six carbons.[102] It is also possible to prepare **34** in a different way, by treating ArCONHPh with PCl_5. The **34** obtained in this way may then be converted to the aldehyde. This is known as the *Sonn-Müller method.*

The other way to reduce nitriles to aldehydes involves use of a metal hydride reducing agent to add one mole of hydrogen, and hydrolysis, *in situ,* of the resulting imine (which is undoubtedly coordinated to the metal). This has been carried out with $LiAlH_4$, $LiAlH(OEt)_3$,[103] $AlH(CH_2CHMe_2)_2$,[104] and $NaAlH_4$.[105] The metal hydride method is useful for aliphatic and aromatic nitriles. Reduction to the aldehyde has also been accomplished by treatment of the nitrile with sodium hypophosphate and Raney nickel in aqueous acetic acid–pyridine or formic acid.[106]

OS **III**, 626, 818.

H. Carbon attack by organometallic compounds

6-31 The addition of organometallic compounds to aldehydes and ketones



$$-\underset{\underset{O}{\|}}{C}- + RMgX \longrightarrow -\overset{R}{\underset{OMgX}{C}}- \xrightarrow{\text{hydrolysis}} -\overset{R}{\underset{OH}{C}}-$$

The addition of Grignard reagents to aldehydes and ketones is known as the *Grignard reaction.* Formaldehyde gives primary alcohols; other aldehydes give secondary alcohols; and ketones give tertiary alcohols. The reaction is of very broad scope, and hundreds of alcohols have been prepared in this manner.[107] Other organometallic compounds may also be used, but only if they are of active metals: e.g., alkylmercurys and alkylcadmiums do not react. In practice, the only organometallic compounds used to any extent, besides Grignard reagents, are alkyl- and aryllithiums, though alkylzinc reagents were used in the past. For the addition of acetylenic groups, sodium may be the metal used: RC≡CNa (reaction **6-41**).

---

[101] For a review, see Mosettig, *Org. Reactions* **8**, 218–257 (1954).

[102] Zil'berman and Pyryalova, *J. Gen. Chem. USSR* **33**, 3348 (1964).

[103] Brown and Shoaf, *J. Am. Chem. Soc.* **86**, 1079 (1964); Brown and Garg, *J. Am. Chem. Soc.* **86**, 1085 (1964).

[104] Miller, Biss, and Schwartzman, *J. Org. Chem.* **24**, 627 (1959).

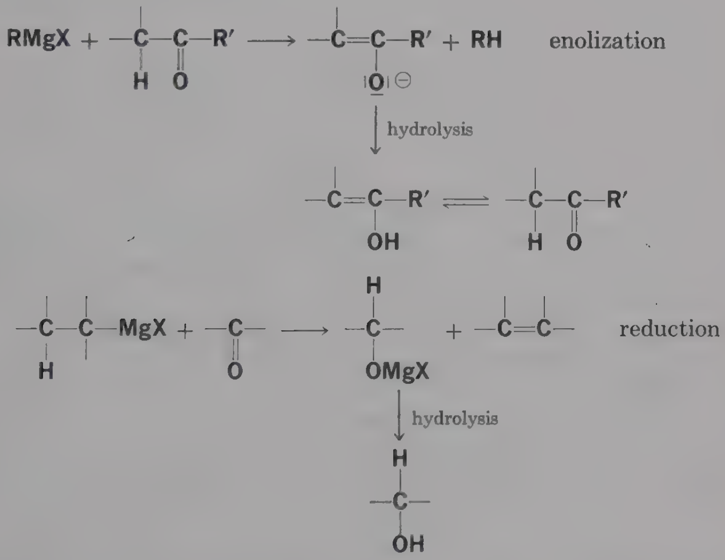
[105] Zakharkin, Maslin, and Gavrilenko, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964**, 1415.

[106] Backeberg and Staskun, *J. Chem. Soc.* **1962**, 3961; Staskun and Backeberg, *J. Chem. Soc.* **1964**, 5880; van Es and Staskun, *J. Chem. Soc.* **1965**, 5775.

[107] For a review, see Kharasch and Reinmuth, "Grignard Reactions of Nonmetallic Substances," pp. 138–528, Prentice-Hall, Inc., Englewood Cliffs, N.J., 1954.

α,β-Unsaturated aldehydes or ketones can give 1,4 addition as well as normal 1,2 addition (see p. 604). In general, alkyllithiums give less 1,4 addition than the corresponding Grignard reagents.[108] Quinones may add Grignard reagents on one or both sides or give 1,4 addition.

Although most aldehydes and ketones react very nicely with most Grignard reagents, there are several types of side reaction which occur mostly with hindered ketones and with bulky Grignard reagents. The two most important of these are *enolization* and *reduction*. The former requires that the aldehyde or ketone have an α hydrogen, and the latter requires that the Grignard reagent have a β hydrogen:



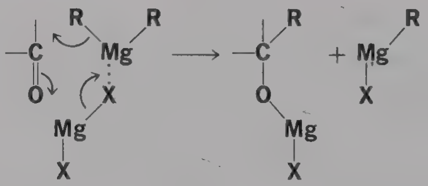
Enolization is an acid-base reaction (**2-14**, p. 470), in which a proton is transferred from the α-carbon to the Grignard reagent. The Grignard reagent RMgX is converted to RH, and the carbonyl compound to its enolate-ion form, which, on hydrolysis, is reconverted to original ketone or aldehyde. Enolization is not only important for hindered ketones, but also for those which have a relatively high percentage of enol form (e.g., β-keto esters, etc.). Another factor which affects enolization is the relative freedom of R in the organometallic compound. Thus, acetophenone gave addition with RMgX and RLi, but enolization with RNa and RK, in which the R has greater carbanionic character.[109] In reduction, the carbonyl compound is reduced to an alcohol (reaction **6-27**) by the Grignard reagent, which itself undergoes elimination to give an olefin. Two other side reactions are condensation (between enolate ion and excess ketone) and Wurtz-type coupling (reaction **0-83**, p. 355). Such highly hindered tertiary alcohols as triisopropylcarbinol, tri-*tert*-butylcarbinol, and diisopropylneopentylcarbinol cannot be prepared (or can be prepared only in extremely low yields) by the addition of Grignard reagents to ketones, because reduction and/or enolization become prominent.[110] However, these carbinols can be prepared by the use of alkyllithiums at −80°,[111] under which conditions enolization and reduction are much less important.

---

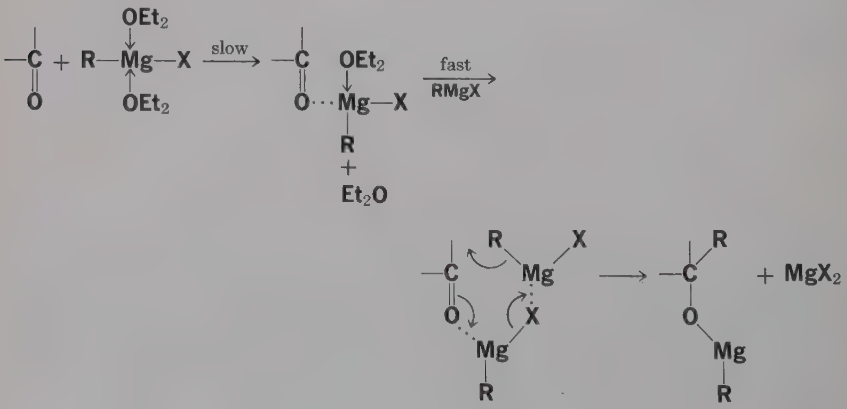
[108] An example was given on p. 605. Another may be found in Wessely, Budzikiewicz, and Janda, *Monatsh. Chem.* **92**, 621 (1961).

[109] O'Sullivan, Swamer, Humphlett, and Hauser, *J. Org. Chem.* **26**, 2306 (1961).

The mechanism of addition of Grignard reagents to aldehydes and ketones is not completely understood.[112] Various cyclic mechanisms have been proposed, some on the basis that the Grignard reagent is RMgX and some on the assumption that the structure is better represented as $R_2Mg{\cdot}MgX_2$ (see pp. 148–151). The following mechanism is based on the latter assumption:[113]



On the other hand, on the basis of the monomeric RMgX now assumed to be present in dilute Grignard solutions (if X = Br or I), the following mechanism has been suggested:[114]



35

---

[110] Whitmore and George, *J. Am. Chem. Soc.* **64**, 1239 (1942).

[111] Bartlett and Lefferts, *J. Am. Chem. Soc.* **77**, 2804 (1955); Zook, March, and Smith, *J. Am. Chem. Soc.* **81**, 1617 (1959).

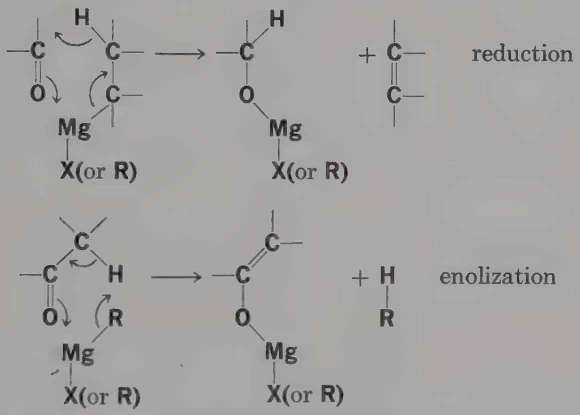
[112] See, for example, D'Hollander and Anteunis, *Bull. Soc. Chim. Belges* **74**, 71 (1965).

[113] Miller, Gregoriou, and Mosher, *J. Am. Chem. Soc.* **83**, 3966 (1961); Bikales and Becker, *Can. J. Chem.* **41**, 1329 (1963). Also see Hamelin, *Bull. Soc. chim. France* **1963**, 1411.

[114] Ashby and Smith, *J. Am. Chem. Soc.* **86**, 4363 (1964). See also Ashby, *Quart. Rev. (London)* **21**, 259–285 (1967).

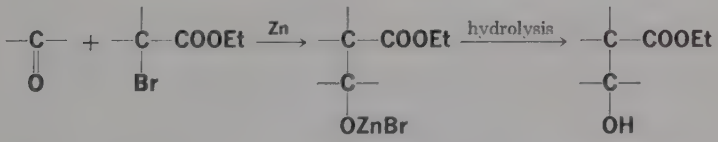
In solutions in which the Grignard reagent is $(RMgX)_2$, there would be only one step, with the C=O group being directly attacked to give the transition state **35.** This mechanism is in agreement with the fact that the rate of Grignard addition is substantially decreased after 50% utilization of the R groups. All mechanisms which have been proposed assume that there is a preliminary formation of a complex between the carbonyl oxygen and the Grignard reagent and that the remaining coordinations of the magnesium (the total is four) are made up by ether molecules of the solvent. There is spectral evidence for such complexes.[115]

There is general agreement that the mechanisms leading to reduction and enolization are also cyclic:



OS **I,** 188; **II,** 406, 606; **III,** 200, 696, 729, 757; **IV,** 771, 792; **41,** 30, 49; **44,** 4.

6-32 The Reformatsky reaction



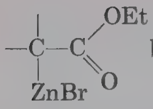
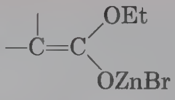
The *Reformatsky reaction* is very similar to reaction **6-31.**[116] An aldehyde or ketone is treated with zinc and a halide; the halide is nearly always an α-halo ester or a vinylog of an α-halo ester (e.g., RCHBrCH=CHCOOEt), though α-halo nitriles[117] and α-halo N,N-disubstituted amides have also been used. The reaction may formally be considered as an addition of an alkylzinc bromide to the carbonyl compound, though this type of intermediate, which would be analogous to the Grignard RMgX, is not present here. There is an intermediate, derived from zinc and the ester, but its structure is not

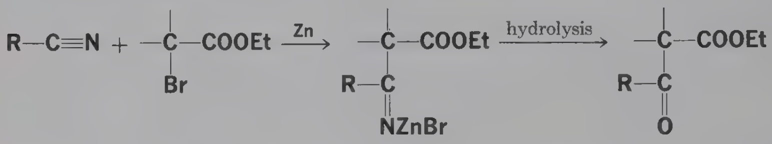
---

[115] Smith, *Tetrahedron Letters* **1963,** 409.

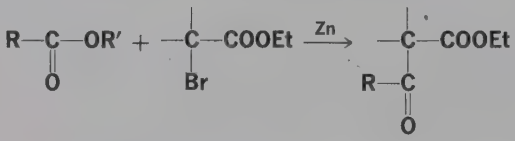
[116] For reviews, see Shriner, *Org. Reactions* **1,** 1–37 (1942); Diaper and Kuksis, *Chem. Rev.* **59,** 89–178 (1959).

[117] Vinograd and Vul'fson, *J. Gen. Chem. USSR* **29,** 248, 1118, 2658, 2659 (1960).


but probably

.[118] Usually, after hydrolysis, the alcohol is the product, but sometimes (especially with aryl aldehydes) elimination follows directly, and the product is an olefin. Since Grignard reagents cannot be formed from α-halo esters, the method is quite useful, although there are competing reactions and yields are sometimes low. A similar reaction has been carried out on nitriles:[119]



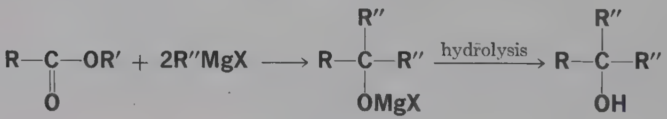
Esters have also been used as substrates, but then, as might be expected (p. 652), the result is substitution and not addition:



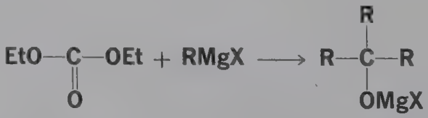
The product in this case is the same as with the corresponding nitrile, though the pathways are different.

OS **III,** 408; **IV,** 120, 444.

6-33 The addition of Grignard reagents to acid derivatives



When esters are treated with Grignard reagents, there is usually concomitant addition to the carbonyl (reaction **6-31**) and substitution of R″ for OR′ (reaction **0-89,** p. 362), so that tertiary alcohols are formed, in which two R groups are the same. Formates give secondary alcohols, and carbonates give tertiary alcohols in which all three R groups are the same:



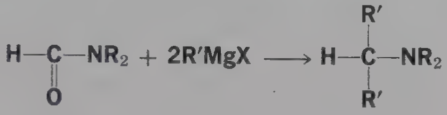
---

[118] Zimmerman and Traxler, *J. Am. Chem. Soc.* **79,** 1920 (1957); Vaughan, Bernstein, and Lorber, *J. Org. Chem.* **30,** 1790 (1965).

[119] Cason, Rinehart, and Thornton, *J. Org. Chem.* **18,** 1594 (1953).

Acyl halides and anhydrides behave similarly, though these substrates are employed less often.[120] There are many side reactions possible, especially when there is branching in the acid derivative or in the Grignard reagent: enolizations, reductions (not for esters, but for halides), condensations, and cleavages, but the most important is simple substitution (reaction **0-89**), which in some cases may be made to predominate.

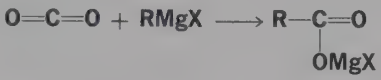
Disubstituted formamides can give addition of two moles of Grignard reagent:[121]



$$H{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}NR_2 + 2R'MgX \longrightarrow H{-}\underset{R'}{\overset{R'}{C}}{-}NR_2$$

OS **I,** 226; **II,** 179, 602; **III,** 237, 831, 839; **IV,** 601.

6-34 The addition of Grignard reagents to CO_2



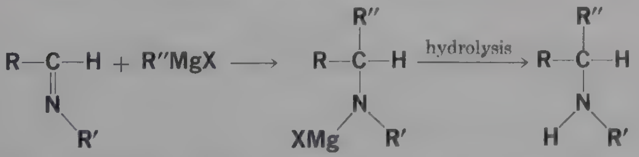
$$O{=}C{=}O + RMgX \longrightarrow R{-}\underset{OMgX}{C}{=}O$$

Grignard reagents add to one C=O bond of CO_2 exactly as they do to an aldehyde or a ketone.[122] Here, of course, the product is the salt of a carboxylic acid. The reaction is usually performed by adding the Grignard reagent to dry ice, but it is also possible to bubble CO_2 through a Grignard solution. However, the latter procedure usually gives lower yields, since the salt can react with additional molecules of Grignard reagent to give a ketone and a tertiary alcohol (reactions **6-31** and **6-33**). Sometimes this can be turned to preparative use; for example, hexamethylacetone can be made in this way from CO_2 and *tert*-butylmagnesium bromide.

Many carboxylic acids have been prepared in this manner, and, along with the **0-87–6-5** sequence and reaction **8-8,** this constitutes an important way of increasing a carbon chain by one unit. Since labeled CO_2 is commercially available, this is a good method for the preparation of carboxylic acids labeled in the carboxyl group. Other organometallic compounds have also been used (RLi, RNa, RCaX, etc.) but much less often. Carbon monoxide gives symmetrical ketones with alkyllithiums: $2RLi + CO \longrightarrow RCOR$.[123]

OS **I,** 361, 524; **II,** 425; **III,** 413, 553, 555; **42,** 97; **44,** 78.

6-35 The addition of Grignard reagents to imines



$$R{-}\underset{\underset{\displaystyle N{-}R'}{\|}}{C}{-}H + R''MgX \longrightarrow R{-}\overset{R''}{\underset{N(MgX)R'}{C}}{-}H \xrightarrow{\text{hydrolysis}} R{-}\overset{R''}{\underset{N(H)R'}{C}}{-}H$$

---

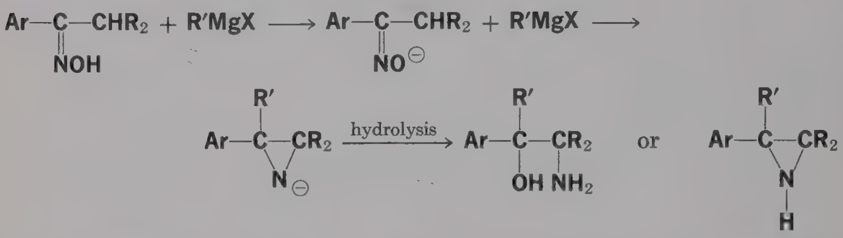
[120] For a review of these reactions, see Ref. 107, pp. 549–766, 846–869.

[121] Kuffner, Sattler-Dornbacher, and Seifried, *Monatsh. Chem.* **93,** 469 (1962).

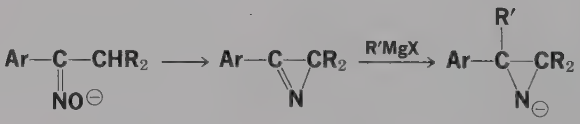
[122] For a review, see Ref. 107, pp. 913–948.

[123] Ryang and Tsutsumi, *Bull. Chem. Soc. Japan* **35,** 1121 (1962); Ryang, Sawa, Hasimoto, and Tsutsumi, *Bull. Chem. Soc. Japan* **37,** 1704 (1964).

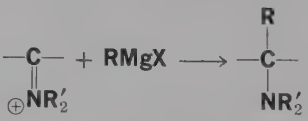
Aldimines may be converted to secondary amines by treatment with Grignard reagents.[124] Ketimines generally give reduction instead of addition. However, organolithium compounds give the normal addition product with both aldimines and ketimines.[125] Many other C=N systems (phenylhydrazones, oxime ethers, etc.) give normal addition when treated with Grignard reagents; others give reduction; others (oximes) give an active hydrogen to the Grignard reagent; and still others give miscellaneous reactions. Aryl alkyl oximes containing an α hydrogen react with two moles of Grignard reagent to give α-amino alcohols, with a net migration of N, or aziridines, depending on the method of hydrolysis:[126]



The mechanism involves initial formation of an azirine (see reaction **8-14**, p. 815):[127]

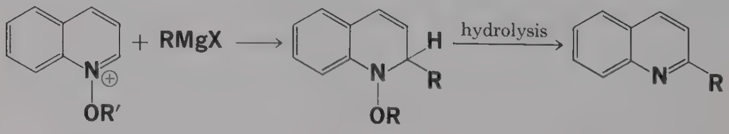


Iminium salts give tertiary amines directly, with just R adding:



$$\underset{\oplus NR'_2}{\overset{}{-\underset{\|}{C}-}} + RMgX \longrightarrow \underset{NR'_2}{\overset{R}{-C-}}$$

Salts of nitrogen heterocycles have also been alkylated in this manner, e.g.,[128]



OS **IV,** 605. Also see OS **III,** 329.

---

[124] For a review of the addition of Grignard reagents to C=N bonds, see Ref. 107, pp. 1204–1227.

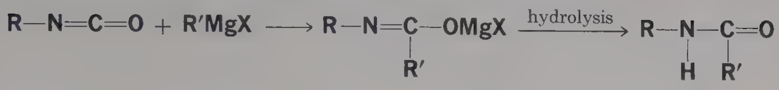
[125] Huet, *Bull. Soc. chim. France* **1964,** 952, 960, 967, 973.

[126] Campbell, Campbell, McKenna, and Chaput, *J. Org. Chem.* **8,** 103 (1943).

[127] Eguchi and Ishii, *Bull. Chem. Soc. Japan* **36,** 1434 (1963).

[128] Červinka, Fábryová, and Matouchová, *Collection Czech. Chem. Commun.* **28,** 535 (1963).

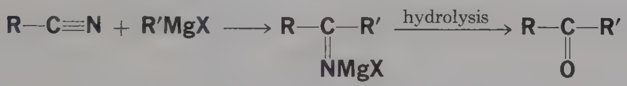
6-36 The addition of Grignard reagents to isocyanates



$$R{-}N{=}C{=}O + R'MgX \longrightarrow R{-}N{=}\underset{\underset{R'}{|}}{C}{-}OMgX \xrightarrow{\text{hydrolysis}} R{-}\underset{\underset{H}{|}}{N}{-}\underset{\underset{R'}{|}}{C}{=}O$$

The addition of Grignard reagents to isocyanates gives, after hydrolysis, N-substituted amides. The reaction is written above as involving addition to C=O, but the ion is a resonance hybrid, and the addition might just as well have been shown as occurring on the C=N. In any event hydrolysis gives the amide. This is a very good reaction and may be used to prepare derivatives of alkyl and aryl halides. Isothiocyanates give N-substituted thioamides.

6-37 The addition of Grignard reagents to nitriles

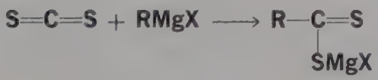


$$R{-}C{\equiv}N + R'MgX \longrightarrow R{-}\underset{\underset{NMgX}{\|}}{C}{-}R' \xrightarrow{\text{hydrolysis}} R{-}\underset{\underset{O}{\|}}{C}{-}R'$$

Ketones may be prepared by addition of Grignard reagents to nitriles and subsequent hydrolysis. Many ketones have been made in this manner, though when both R groups are alkyl, yields are not high.[129] The ketimine salt does not in general react with Grignard reagents; hence tertiary alcohols or tertiary alkyl amines are not often side products. By careful hydrolysis of the salt it is sometimes possible to isolate ketimines $R{-}\underset{\underset{NH}{\|}}{C}{-}R'$.[130] The addition of Grignard reagents to the C≡N group is normally slower than to the C=O group, and CN-containing aldehydes add the Grignard reagent without disturbing the CN group.[131]

OS **III,** 26, 562; **44,** 51.

6-38 The addition of Grignard reagents to CS_2



$$S{=}C{=}S + RMgX \longrightarrow R{-}\underset{\underset{SMgX}{|}}{C}{=}S$$

This reaction is analogous to reaction **6-34.**

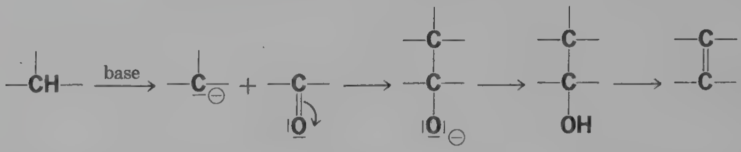
I. Carbon attack by active hydrogen compounds. Reactions **6-39** through **6-46** are base-catalyzed condensations (although some of them are catalyzed by acids too). In reactions **6-39** through **6-45,** a base removes a C—H proton to give a carbanion, which then adds to a C=O. The oxygen acquires a proton, and the resulting alcohol may or may not be dehydrated, depending on whether an α hydrogen is present and on whether the new double bond would be in conjugation with double bonds already present:

---

[129] For a review, see Ref. 107, pp. 767–845.

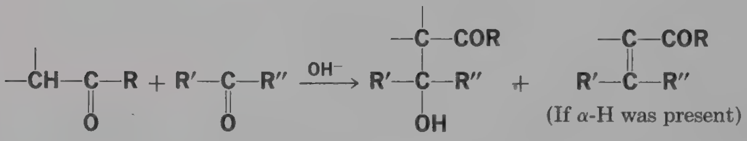
[130] Pickard and Tolbert, *J. Org. Chem.* **26,** 4886 (1961).

[131] Cason, Kraus, and McLeod, *J. Org. Chem.* **24,** 392 (1959).

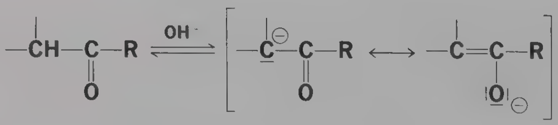


The reactions differ in the nature of the active hydrogen component and of the carbonyl component. Table 2 illustrates the differences. Reaction **6-46** is an analogous reaction involving addition to C≡N.

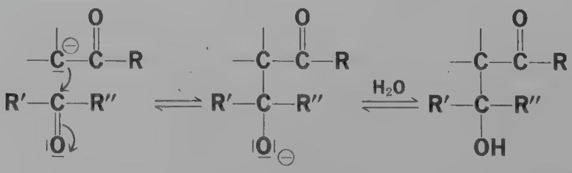
6-39 The aldol condensation



In the *aldol condensation* the α-carbon of one aldehyde or ketone molecule adds to the carbonyl carbon of another. The base most often used is OH⁻, though stronger bases (e.g., aluminum *tert*-butoxide) are sometimes employed. Hydroxide ion is not a strong enough base to convert substantially all of an aldehyde or ketone molecule to the corresponding enolate ion; that is, the equilibrium



lies well to the left, for both aldehydes and ketones. Nevertheless, enough enolate ion is present for the reaction to proceed:

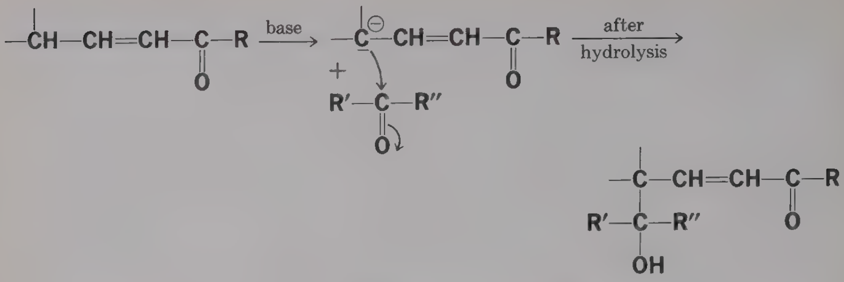


The product is a β-hydroxy aldehyde (called an *aldol*) or ketone, which in some cases is dehydrated during the course of the reaction. Even if the

TABLE 2. A list of the base-catalyzed condensations showing the active-hydrogen components and the carbonyl components

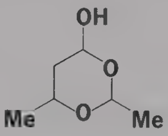
Reaction	*Active-hydrogen component*	*Carbonyl component*	*Subsequent reactions*
6-39 Aldol condensation	Aldehyde $-\overset{\vert}{\mathrm{CH}}-\mathrm{CHO}$ Ketone $-\underset{\vert}{\mathrm{CH}}-\mathrm{COR}$	Aldehyde, ketone	Dehydration may follow
6-40	Ester $-\overset{\vert}{\mathrm{CH}}-\mathrm{COOR}$	Aldehyde, ketone (usually without α hydrogens)	Dehydration may follow
6-41 Knoevenagel reaction	$\mathrm{Z-CH_2-Z'}$, $\mathrm{Z-CHR-Z'}$, and similar molecules	Aldehyde, ketone (usually without α hydrogens)	Dehydration usually follows
6-42 Perkin reaction	Anhydride $-\dot{\mathrm{C}}\mathrm{H}-\mathrm{COOCOR}$	Aromatic aldehyde	Dehydration usually follows
6-43 Darzen's reaction	α-halo ester $\mathrm{X}\overset{\vert}{\mathrm{CH}}-\mathrm{COOR}$	Aldehyde, ketone	Epoxidation (S_N reaction) follows
6-44 Tollen's reaction	Aldehyde $-\overset{\vert}{\mathrm{CH}}-\mathrm{CHO}$ Ketone $-\overset{\vert}{\mathrm{CH}}-\mathrm{COR}$	Formaldehyde	Crossed Cannizzaro reaction follows
6-45 Wittig reaction	Phosphorus ylide $\mathrm{Ph_3}\overset{\oplus}{\mathrm{P}}-\underset{\ominus}{\overset{\vert}{\mathrm{C}}}-$	Aldehyde, ketone	"Dehydration" always follows
6-46 Thorpe reaction	Nitrile$-\overset{\vert}{\mathrm{CH}}-\mathrm{CN}$	Nitrile	

dehydration is not spontaneous, it can usually easily be done, since the new double bond will be in conjugation with the C=O bond, so that this is a method of preparing α,β-unsaturated aldehydes and ketones, as well as β-hydroxy aldehydes and ketones. The entire reaction is an equilibrium (including the dehydration step), and α,β-unsaturated and β-hydroxy aldehydes and ketones may be cleaved by treatment with OH^-. Under the principle of vinylology, the active hydrogen may be one in the γ position of an α,β-unsaturated carbonyl compound:



The scope of the aldol condensation may be discussed under five headings:

1. *Condensation between two molecules of the same aldehyde.* This equilibrium lies far over to the right, and the reaction is quite feasible. Many aldehydes have been converted to aldols and their dehydration products in this manner. Of course, the aldehyde must be one that has an α hydrogen. Aldol itself, the condensation product of acetaldehyde, is actually a trimer:[132]



2. *Condensation between two molecules of the same ketone.* In this case, the equilibrium lies well over to the left, and the reaction is feasible only if the equilibrium can be shifted. This can often be done by allowing the reaction to proceed in a Soxhlet extractor (for example, see OS **I**, 199). In this method the ketone is refluxed in such a way that the condensate drips into a separate chamber, in which is present the base. In this chamber the reaction proceeds to the small extent permitted by the unfavorable equilibrium. When the chamber is full, the mixture of the ketone and its dimer is siphoned back into the original flask, out of contact with the base. Since the boiling point of the dimer is higher than that of the ketone, only the ketone is volatilized back to the chamber containing the base, where a little more of it is converted to dimer, and the process is repeated until a reasonable yield of dimer is obtained. Only methyl ketones have been satisfactorily condensed, and the active hydrogen usually comes from the methyl group. (However, with *acid* catalysts, the active hydrogen comes from the other side.)

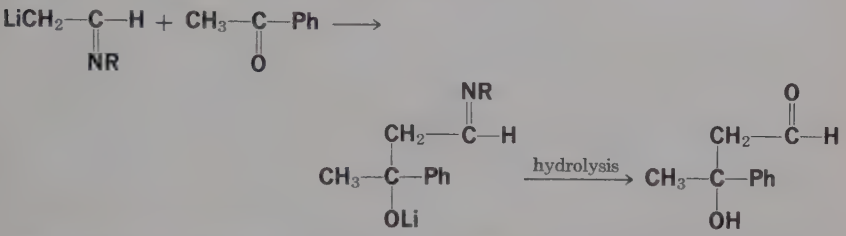
3. *Condensation between two different aldehydes.* In the most general case this will produce a mixture of four products (eight, if the olefins are counted). However, if one aldehyde does not have an α hydrogen, then only two aldols are possible, and in many cases the crossed product is the main one. The crossed aldol condensation is often called the *Claisen-Schmidt reaction.*

4. *Condensation between two different ketones.* This is seldom attempted, but similar considerations apply.

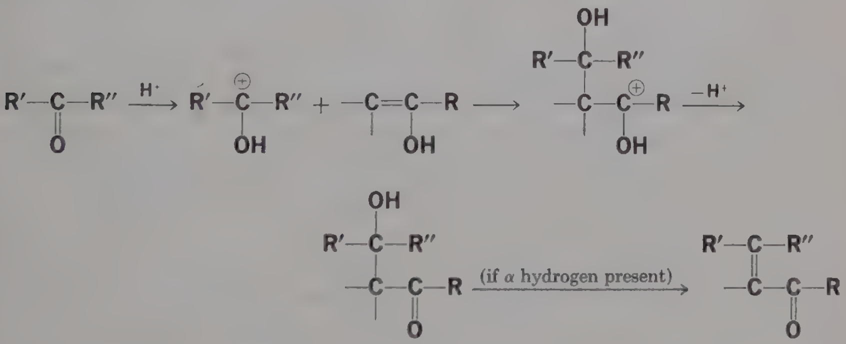
---

[132] Gruen and McTigue, *Australian J. Chem.* **17**, 953 (1964).

5. *Condensation between an aldehyde and a ketone.* This is usually feasible, especially when the aldehyde has no α hydrogen, since there is no competition from ketone condensing with itself. This is also called the *Claisen-Schmidt reaction.* Even when the aldehyde has an α hydrogen, it is the α-carbon of the ketone which adds to the carbonyl of the aldehyde, and not the other way around. It is possible to make the α-carbon of the aldehyde add to the carbonyl carbon of the ketone, by using the Schiff base instead of the aldehyde, and $LiNEt_2$ as the base:[133]



The aldol condensation may also be performed with acid catalysts, in which case dehydration usually follows. Here there is initial protonation of the carbonyl group, which attacks the α-carbon of the *enol* form of the other molecule:



With respect to the enol, this mechanism is similar to that of α halogenation (reaction **2-4,** p. 458). As indicated earlier, if an aldehyde condenses with a methyl ketone, acid and basic catalysts give different products. An example is the condensation of benzaldehyde with butanone, in which the aldehyde condenses with the methyl group with a basic catalyst, but with the methylene with an acid catalyst.[134]

A side reaction which is sometimes troublesome is further condensation, since the product of an aldol condensation is still an aldehyde or ketone.

Aldol condensations are often used for ring closure.

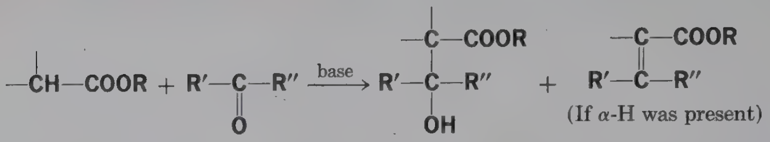
OS **I,** 77, 78, 81, 199, 283, 341; **II,** 167, 214; **III,** 317, 353, 367, 747, 806, 829; **41,** 38; **45,** 80.

---

[133] Wittig, Frommeld, and Suchanek, *Angew. Chem. Intern. Ed. Engl.* **2,** 683 (1963). For a review, see Wittig, *Rec. Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) **28,** 45–60 (1967).

[134] Gettler and Hammett, *J. Am. Chem. Soc.* **65,** 1824 (1943).

6-40 Condensations between esters and aldehydes or ketones



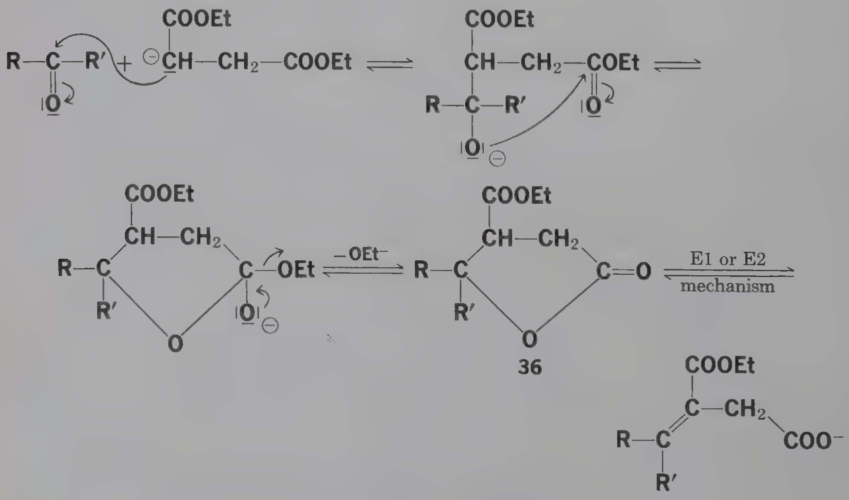
$$-\overset{|}{C}H-COOR + R'-\underset{\underset{O}{\|}}{C}-R'' \xrightarrow{\text{base}} R'-\underset{\underset{OH}{|}}{\overset{\overset{|}{-C-COOR}}{\overset{|}{C}}}-R'' + R'-\overset{-C-COOR}{\overset{\|}{C}}-R''$$

(If α-H was present)

In the presence of a strong base, the α-carbon of an ester may condense with the carbonyl carbon of an aldehyde or ketone to give a β-hydroxy ester, which may or may not be dehydrated to the α,β-unsaturated ester. This reaction is sometimes called the Claisen condensation, but this is an unfortunate usage, since that name is more firmly connected to reaction **0-93** (p. 366). It is also possible for the α-carbon of an aldehyde or ketone to add to the carbonyl carbon of an ester, but this is a different reaction (**0-94**) involving nucleophilic substitution and not addition to a C=O bond. It can, however, be a side reaction if the aldehyde or ketone has an α hydrogen.

Besides ordinary esters (containing an α hydrogen), the reaction may also be carried out with lactones and, as in reaction **6-39**, with the γ position of α,β-unsaturated esters (vinylology).

For most esters, a much stronger base is needed than for aldol condensations: Ph_3CNa and $LiNH_2$[135] are among those employed. However, one type of ester reacts more easily, and such strong bases are not needed: diethyl succinate and its derivatives condense with aldehydes and ketones in the presence of bases such as NaOEt, NaH, or $KOCMe_3$. This reaction is called the *Stobbe condensation.*[136] One of the ester groups, and sometimes both, is hydrolyzed in the course of the reaction. The following mechanism accounts for (1) the fact that succinic esters react so much better than others; (2) one ester group is always cleaved; and (3) the alcohol is not the product, but the olefin. In addition, intermediate lactones **36** have been isolated from the mixture:[137]



---

[135] Dunnavant and Hauser, *J. Org. Chem.* **25**, 503, 1693 (1960).

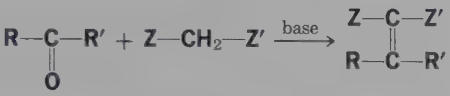
[136] For a review, see Johnson and Daub, *Org. Reactions* **6**, 1–73 (1951).

[137] Robinson and Seijo, *J. Chem. Soc.* **1941**, 582.

The Stobbe condensation has been extended to di-*tert*-butyl esters of glutaric acid.[138]

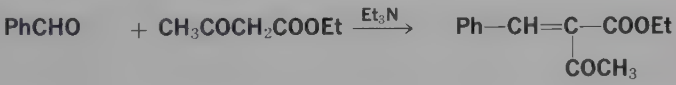
OS **I**, 252; **III**, 132; **43**, 3; **44**, 56. Also see OS **IV**, 278, 478; **46**, 28.

6-41 The Knoevenagel condensation



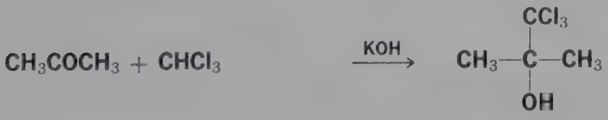
$$R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}R' + Z{-}CH_2{-}Z' \xrightarrow{\text{base}} \begin{matrix} Z{-}C{-}Z' \\ \| \\ R{-}C{-}R' \end{matrix}$$

The condensation of aldehydes or ketones, usually not containing an α hydrogen, with compounds of the form Z—CH$_2$—Z′ or Z—CHR—Z′ is usually called the *Knoevenagel reaction*,[138a] although some limit the use of this name to only some of the active-hydrogen compounds which give the reaction. Z and Z′ may be CHO, COR, COOR, CN, NO$_2$, SOR, SO$_2$R, SO$_2$OR, or similar groups. Other active hydrogen compounds also may be employed, among them CHCl$_3$, 2-methylpyridines, terminal acetylenes, cyclopentadienes, etc.; in fact any compound which contains a C—H bond, the hydrogen of which can be removed by a base. Some examples are

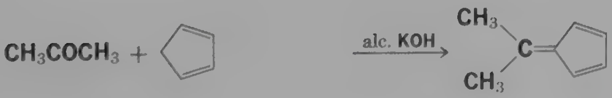


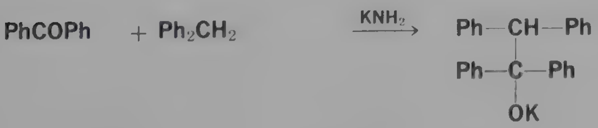
$$PhCHO + CH_3COCH_2COOEt \xrightarrow{Et_3N} Ph{-}CH{=}\underset{\displaystyle COCH_3}{\underset{|}{C}}{-}COOEt$$

$$PhCHO + CH_3NO_2 \xrightarrow{NaOH} Ph{-}CH{=}CH{-}NO_2$$



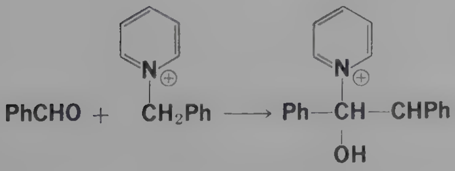
$$CH_3COCH_3 + CHCl_3 \xrightarrow{KOH} CH_3{-}\overset{\displaystyle CCl_3}{\underset{\displaystyle OH}{C}}{-}CH_3$$





$$PhCOPh + Ph_2CH_2 \xrightarrow{KNH_2} \begin{matrix} Ph{-}CH{-}Ph \\ | \\ Ph{-}C{-}Ph \\ | \\ OK \end{matrix}$$

(Ref. 139)



(Ref. 140)

---

[138] Puterbaugh, *J. Org. Chem.* **27**, 4010 (1962).

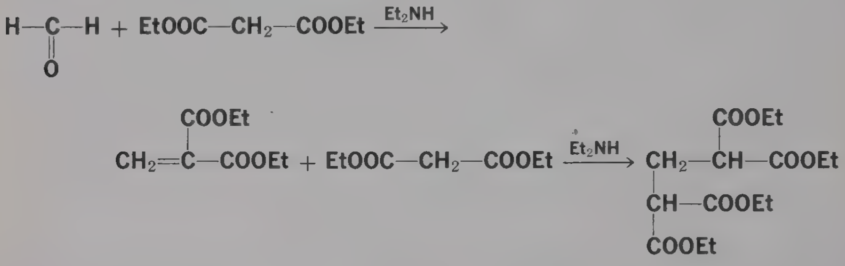
[138a] For a review, see Jones, *Org. Reactions* **15**, 204–599 (1967).

[139] Hamrick and Hauser, *J. Am. Chem. Soc.* **81**, 2096, 3144 (1959).

[140] For a review of these reactions with pyridinium salts, see Kröhnke, *Angew. Chem. Intern. Ed. Engl.* **2**, 225–237 (1963).

The reaction with cyclopentadiene is a good method for the preparation of fulvenes. The reaction with terminal acetylenes is called the *Favorskii reaction,* not to be confused with the *Favorskii rearrangement* (reaction **8-7,** p. 804).

With most of these reagents the alcohol is not isolated, but only the olefin, if the alcohol has a hydrogen in the proper position. However, in some cases it is the alcohol which is the major product. When the reactant is of the form ZCH_2Z', aldehydes react much better than ketones. The base in these cases is usually a tertiary amine; when it is pyridine, the reaction is called the *Doebner modification* of the Knoevenagel reaction. In some cases amine salts make better catalysts than the free amines, but this is not always true. Alkoxides are also common catalysts. In some cases it is possible to get a second molecule of active compound to add to the initial product, in a Michael reaction; e.g.,



$$H\text{—}\underset{\underset{O}{\|}}{C}\text{—}H + EtOOC\text{—}CH_2\text{—}COOEt \xrightarrow{Et_2NH}$$

$$CH_2\text{=}\overset{\overset{COOEt}{|}}{C}\text{—}COOEt + EtOOC\text{—}CH_2\text{—}COOEt \xrightarrow{Et_2NH} \underset{\underset{\underset{COOEt}{|}}{CH\text{—}COOEt}}{\overset{}{CH_2}}\text{—}\overset{\overset{COOEt}{|}}{CH}\text{—}COOEt$$

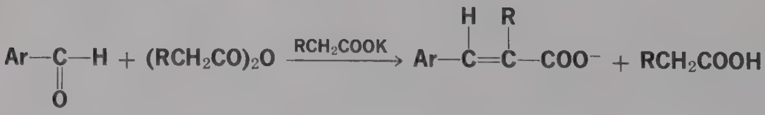
It has also proved possible to have one active hydrogen compound add to an aldehyde and then, *in situ,* to have a *different* one add to the olefin in the Michael manner.[141]

As with reaction **6-39,** these reactions have sometimes been performed with acid catalysts.[142]

Imines may be employed instead of aldehydes or ketones; the products are the same, an amine being lost instead of water.[143]

OS **I,** 181, 290, 413; **II,** 202; **III,** 39, 165, 317, 320, 377, 385, 399, 416, 425, 456, 479, 513, 586, 591, 597, 715, 783; **IV,** 93, 210, 221, 234, 293, 327, 387, 392, 408, 441, 463, 471, 549, 573, 730, 731, 777; **40,** 27, 46; **41,** 67; **43,** 49; **44,** 59, 94. Also see OS **III,** 395.

6-42 The Perkin reaction



$$Ar\text{—}\underset{\underset{O}{\|}}{C}\text{—}H + (RCH_2CO)_2O \xrightarrow{RCH_2COOK} Ar\text{—}\overset{\overset{H}{|}}{C}\text{=}\overset{\overset{R}{|}}{C}\text{—}COO^- + RCH_2COOH$$

The condensation of aromatic aldehydes with anhydrides is called the *Perkin reaction.*[144] When the anhydride has two α hydrogens (as shown), dehydration always occurs—the β-hydroxy acid salt is never isolated. In some cases, anhydrides of the form $(R_2CHCO)_2O$ have been used, and then the hydroxy compound is the product, since dehydration cannot take place. The base in the Perkin reaction is nearly always the sodium or potassium salt of the acid corresponding to the anhydride. For many years there was controversy as to whether it was the anhydride or the salt which was adding to the aldehyde. The obvious way to settle the matter would be to use an anhydride of one acid and a salt of another, but early investigators were misled because they failed to take into account the equilibrium between the salt and the anhydride. It is now generally accepted that it is the anhydride which condenses. Indeed, it should be easier to remove an α hydrogen from an anhydride than from a salt, because of the inductive effect of the COO^- group. Besides aromatic aldehydes, their vinylogs, $ArCH{=}CHCHO$, also give the reaction. Otherwise, the reaction is not suitable for aliphatic aldehydes.[145] There is a possible side reaction: decarboxylation of the initial β-hydroxy acid salt instead of simple dehydration. Sometimes this is the main reaction:

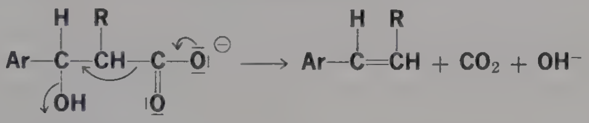
---

[141] For example, see Russell and Becker, *J. Am. Chem. Soc.* **85,** 3406 (1963).

[142] For example, see Rappoport and Patai, *J. Chem. Soc.* **1962,** 731.

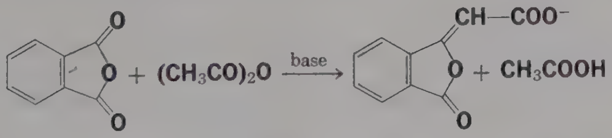
[143] Charles, *Bull. Soc. chim. France* **1963,** 1559, 1566, 1573, 1576.

[144] For a review of the Perkin reaction and the related Erlenmeyer synthesis, see Johnson, *Org. Reactions* **1,** 210–266 (1942).

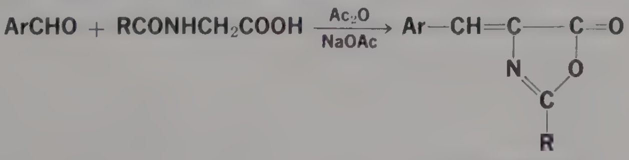


$$\mathrm{Ar{-}\overset{H}{\underset{OH}{C}}{-}\overset{R}{C}H{-}\underset{\overset{\|}{O}}{C}{-}\underline{\bar{O}}|^{\ominus}} \longrightarrow \mathrm{Ar{-}\overset{H}{C}{=}\overset{R}{C}H + CO_2 + OH^-}$$

Phthalic anhydride and its derivatives may participate in the Perkin reaction as the carbonyl component, e.g.,

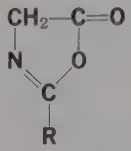


An important variation of the Perkin reaction is the *Erlenmeyer azlactone* synthesis.[146] In this reaction aromatic aldehydes are condensed with N-acyl derivatives of glycine, in the presence of acetic anhydride and sodium acetate. The product is an azlactone:



An azlactone

It is likely that **37** is formed first, and then condenses with the aldehyde.



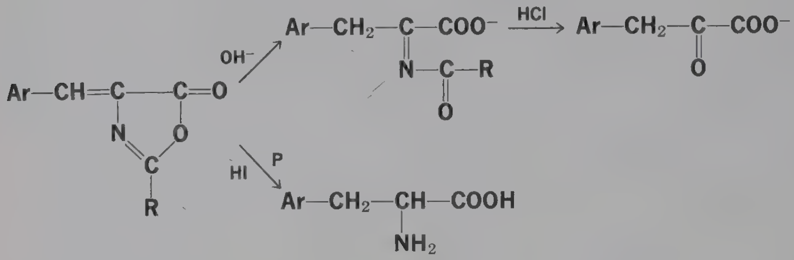
37

---

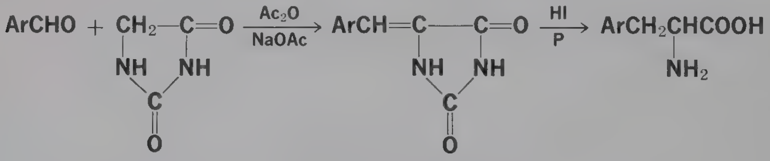
[145] Crawford and Little, *J. Chem. Soc.* **1959,** 722.

[146] For reviews, see Ref. 145; Carter, *Org. Reactions* **3,** 198–239 (1946); and Baltazzi, *Quart. Rev. (London)* **9,** 150–173 (1955).

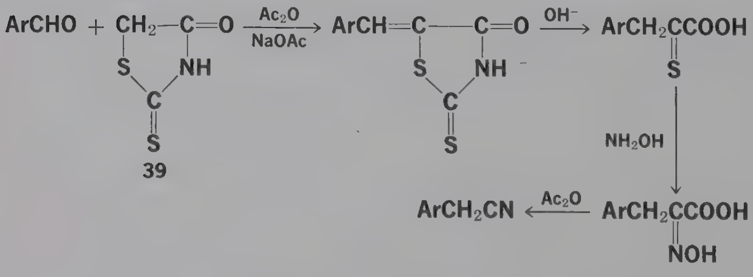
When **37** was prepared independently, it reacted with aromatic aldehydes to give azlactones.[147] Interestingly, aliphatic aldehydes and ketones also reacted with **37**. Azlactones are useful because they can be converted into other compounds. Treatment with NaOH, followed by HCl, gives arylpyruvic acids, the preparation of which represents a method of increasing the carbon chain by two (from the original aldehyde). Reduction of an azlactone by phosphorus and HI, or other reducing agents, produces an amino acid, also increasing the chain by two:



Further variations of the Perkin reaction involve condensation with hydantoin (**38**) and with rhodanine (**39**). The product from hydantoin condensation may also be reduced to an amino acid. The product from the rhodanine condensation may be converted, in high yield, by a three-step process to a nitrile with one more carbon than the original aldehyde:



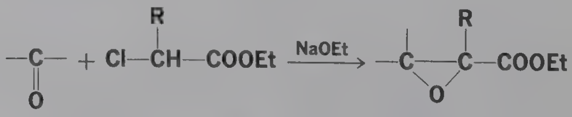
38



39

OS **I**, 398; **II**, 1, 55, 61, 229; **III**, 426. Also see OS **II**, 333, 519.

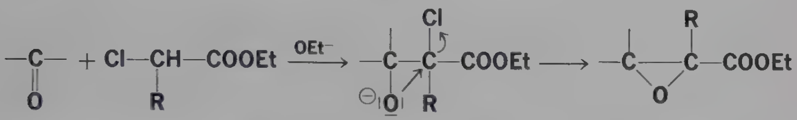
6-43 Darzen's glycidic ester condensation



---

[147] Crawford and Little, *J. Chem. Soc.* **1959**, 729.

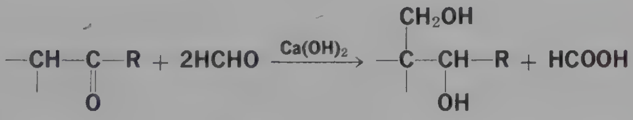
Aldehydes and ketones condense with α-halo esters in the presence of bases to give α,β-epoxy esters, called *glycidic esters*. This is called *Darzen's condensation*.[148] Aliphatic aldehydes give poor yields. Sodium ethoxide is often used as the base, though other bases, including sodium amide, are sometimes used. The reaction consists of an initial Knoevenagel-type condensation (**6-41**) followed by an internal S_N2 reaction (**0-17**, p. 316):



Although the intermediate halo alkoxide is generally not isolated, it has been done, not only with α-fluoro esters (since fluorine is such a poor leaving group in nucleophilic substitutions) but also with α-chloro esters.[149] This is only one of several types of evidence that rule out a carbene intermediate.[150] Similar reactions have been carried out on α-halo ketones, α-halo nitriles, α-halo di-N-substituted amides,[151] and even on benzylic halides. Glycidic esters may be easily converted to aldehydes (reaction **2-26**, p. 477). Also see reaction **6-62**.

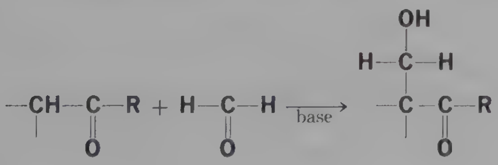
OS **III**, 727; **IV**, 459, 649.

6-44 Tollen's reaction



$$-\underset{|}{CH}-\underset{O}{\underset{\|}{C}}-R + 2HCHO \xrightarrow{Ca(OH)_2} -\overset{CH_2OH}{\overset{|}{\underset{|}{C}}}-\underset{OH}{\underset{|}{CH}}-R + HCOOH$$

In *Tollen's reaction* an aldehyde or ketone containing an α hydrogen is treated with formaldehyde in the presence of $Ca(OH)_2$ or a similar base. The first step is a mixed aldol condensation (**6-39**), in which the α-carbon of the aldehyde or ketone adds to the carbonyl carbon of formaldehyde:



$$-\underset{|}{CH}-\underset{O}{\underset{\|}{C}}-R + H-\underset{O}{\underset{\|}{C}}-H \xrightarrow[\text{base}]{} -\overset{\overset{OH}{|}}{\overset{H-C-H}{\overset{|}{\underset{|}{C}}}}-\underset{O}{\underset{\|}{C}}-R$$

The reaction may be stopped at this point, but more often a second mole of formaldehyde is permitted to reduce the newly formed aldol to a 1,3-glycol, in a crossed Cannizzaro reaction (**9-62**, p. 908). If the aldehyde or ketone has several α hydrogens, they may all be replaced, one at a time. An important use of the reaction is to prepare pentaerythritol from acetaldehyde:

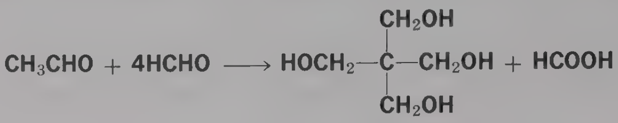
---

[148] For reviews, see Newman and Magerlein, *Org. Reactions* **5**, 413–440 (1949); Ballester, *Chem. Rev.* **55**, 283–300 (1955).

[149] Martynov and Titov, *J. Gen. Chem. USSR* **30**, 4072 (1960), **32**, 716 (1962), **33**, 1350 (1963), **34**, 2139 (1964).

[150] Another, based on the stereochemistry of the products, is described by Zimmerman and Ahramjian, *J. Am. Chem. Soc.* **82**, 5459 (1960).

[151] Tung, Speziale, and Frazier, *J. Org. Chem.* **28**, 1514 (1963).



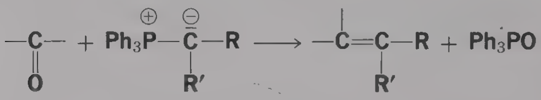
$$CH_3CHO + 4HCHO \longrightarrow HOCH_2-\overset{\displaystyle CH_2OH}{\underset{\displaystyle CH_2OH}{C}}-CH_2OH + HCOOH$$

When aliphatic nitro compounds are used instead of aldehydes or ketones, no reduction occurs, and the reaction is essentially a Knoevenagel reaction, though it is usually also called a Tollen's reaction:

$$CH_3NO_2 + HCHO \xrightarrow{OH^-} HOCH_2CH_2NO_2$$

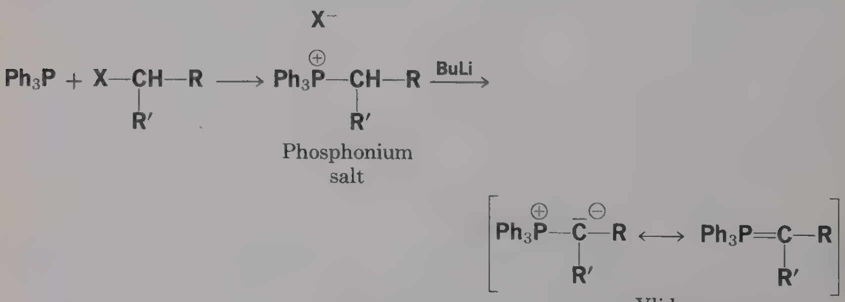
OS **I,** 425; **IV,** 907; **41,** 67.

6-45 The Wittig reaction



$$-\underset{\displaystyle O}{\overset{}{\underset{\|}{C}}}- + Ph_3\overset{\oplus}{P}-\underset{\displaystyle R'}{\overset{\ominus}{\underset{|}{\bar{C}}}}-R \longrightarrow -\overset{|}{C}=\underset{\displaystyle R'}{\underset{|}{C}}-R + Ph_3PO$$

In the *Wittig reaction* an aldehyde or ketone is treated with a *phosphorus ylide* (also called a *phosphorane*) to give an olefin.[152] Phosphorus ylides, which are hybrids of two canonical forms, are most often prepared by treatment of a phosphonium salt with a base; and phosphonium salts are most often prepared from the phosphine and an alkyl halide (reaction **0-44**, p. 331):



$$Ph_3P + X-\underset{\displaystyle R'}{\underset{|}{CH}}-R \longrightarrow Ph_3\overset{\overset{\displaystyle X^-}{\oplus}}{P}-\underset{\displaystyle R'}{\underset{|}{CH}}-R \xrightarrow{BuLi} \left[Ph_3\overset{\oplus}{P}-\underset{\displaystyle R'}{\overset{\ominus}{\underset{|}{\bar{C}}}}-R \longleftrightarrow Ph_3P=\underset{\displaystyle R'}{\underset{|}{C}}-R\right]$$

Phosphonium salt

Ylide

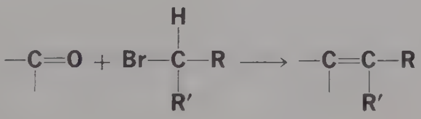
---

[152] For reviews, see Maerker, *Org. Reactions* **14**, 270–490 (1965); Trippett, *Quart. Rev.* (*London*) **17**, 406–440 (1963); *Advan. Org. Chem.* **1**, 83–102 (1960); *Pure Appl. Chem.* **9**, 255–269 (1964); Schöllkopf, in Foerst, "Newer Methods of Pure and Applied Chemistry," vol. 3, pp. 111–150, Academic Press Inc., New York, 1964 [this review also appears in *Angew. Chem.* **71**, 260 (1959)]; Yanovskaya, *Russ. Chem. Rev.* **30**, 347–362 (1961); and House, "Modern Synthetic Reactions," pp. 245–256, W. A. Benjamin, Inc., New York, 1965. For a historical background, see Wittig, *Pure Appl. Chem.* **9**, 245–254 (1964).

The overall sequence of three steps may be called the Wittig reaction, or only the final step. Phosphonium salts are also prepared by addition of phosphines to Michael olefins (like reaction **5-9**, p. 589) and in other ways. The phosphonium salts are most often converted to the ylides by treatment with butyllithium, though weaker bases may be used if the salt is acidic enough. For $(Ph_3P^+)_2CH_2$, sodium carbonate is a strong enough base.[153] The conversion of phosphonium salts to ylides is apparently a simple acid-base reaction (**2-12**, p. 468), but, at least with alkyllithiums, it must be more complicated than that, since, in addition to a simple proton abstraction, exchange of groups can occur. Thus, $Ph_3\overset{\oplus}{P}CH_3\ \ Br^-$ with methyllithium gave 26% *benzene*.[154] It is likely that an intermediate Ph_3PMe_2 was formed, which lost either methane or benzene to give an ylide. Phosphorus ylides may also be prepared by the addition of halocarbenes to phosphines in a Lewis acid-base reaction:

$$\bar{C}HCl + Ph_3P \longrightarrow Ph_3\overset{\oplus}{P}\overset{\ominus}{\bar{C}}HCl$$

In the overall Wittig reaction, an olefin is formed from the aldehyde or ketone and an alkyl halide in which the halogen-bearing carbon contains at least one hydrogen:



$$-\underset{|}{C}=O + Br-\overset{\overset{H}{|}}{\underset{\underset{R'}{|}}{C}}-R \longrightarrow -\underset{|}{C}=\underset{\underset{R'}{|}}{C}-R$$

This result is similar to that obtained in the Reformatsky reaction (**6-32**), but this is more general since no ester or other group is required to be α to the halogen. Another important advantage of the Wittig reaction is that the *position* of the new double bond is always certain, in contrast to the result in the Reformatsky reaction and in most of the base-catalyzed condensations (**6-39** to **6-44**).

The reaction is very general. The aldehyde or ketone may be aliphatic, alicyclic, or aromatic (including diaryl ketones); it may contain double or triple bonds; it may contain various functional groups, such as OH, OR, NR_2, aromatic nitro or halo, acetal, or even ester groups. Although phosphorus ylides also react with esters (reaction **0-95**, p. 369), that reaction is too slow to interfere.[155] Double or triple bonds *conjugated* with the carbonyl also do not interfere, the attack being at the C=O carbon.

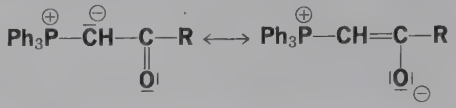
The phosphorus ylide may also contain double or triple bonds and certain functional groups. Simple ylides (R, R′ = hydrogen or alkyl) are highly reactive, reacting with oxygen, water, hydrohalic acids, and alcohols, as well as carbonyl compounds and esters, so that the reaction must be run under conditions where these materials are absent. When an electron-withdrawing group (for example, COR, CN, COOR, CHO) is present in the α position, the ylides are much more stable. The stability is increased because the charge on the carbon is spread by resonance:

---

[153] Ramirez, Desai, Hansen, and McKelvie, *J. Am. Chem. Soc.* **83**, 3539 (1961).

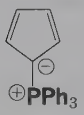
[154] Seyferth, Hughes, and Heeren, *J. Am. Chem. Soc.* **87**, 2847, 3467 (1965).

[155] Greenwald, Chaykovsky, and Corey, *J. Org. Chem.* **28**, 1128 (1963).



$$\mathrm{Ph_3\overset{\oplus}{P}{-}\overset{\ominus}{\bar{C}}H{-}\underset{\underset{\bar{O}|}{\|}}{C}{-}R \longleftrightarrow Ph_3\overset{\oplus}{P}{-}CH{=}\underset{\underset{|\bar{O}|^{\ominus}}{|}}{C}{-}R}$$

These ylides react readily with aldehydes, but slowly or not at all with ketones. In extreme cases (e.g., compound **40**) the ylide does not react with ketones *or* aldehydes. Besides these groups, the ylide may contain one or

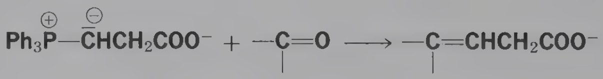


40

two α halogens [these ylides may be prepared from halocarbenes and phosphines (p. 703) or in the normal manner][156] or an α OR or OAr group. In the latter case, the product is an enol ether. However, the ylide may not contain an α nitro group. If the phosphonium salt contains a potential leaving group, such as Br or OMe, in the β position, then treatment with a base gives elimination, instead of the ylide:

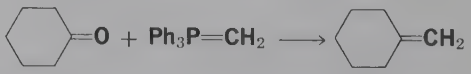
$$\mathrm{Ph_3\overset{\oplus}{P}CH_2CH_2Br \xrightarrow{base} Ph_3\overset{\oplus}{P}CH{=}CH_2}$$

However, a β-COO$^-$ group may be present, and the product is a β,γ-unsaturated acid.[157]



$$\mathrm{Ph_3\overset{\oplus}{P}{-}\overset{\ominus}{\bar{C}}HCH_2COO^- + {-}\underset{|}{C}{=}O \longrightarrow {-}\underset{|}{C}{=}CHCH_2COO^-}$$

This is the only convenient way to make these compounds, since elimination by any other route gives the thermodynamically more stable α,β-unsaturated isomers. This is an illustration of the utility of the Wittig method for the specific location of a double bond. Another illustration is the conversion of cyclohexanones to olefins containing exocyclic double bonds, e.g.,[158]



This is the only general method for the synthesis of these compounds.

Ylides are most often prepared from triphenylphosphine, but trialkylphosphines[159] and triphenylarsine have also been used. The Wittig reaction has also been carried out with other types of ylides, the most important being prepared from phosphonates:[160]

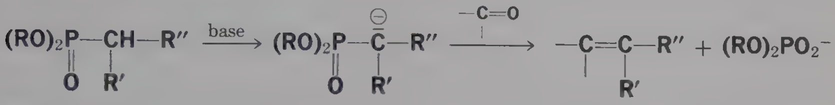
---

[156] Seyferth, Grim, and Read, *J. Am. Chem. Soc.* **82,** 1510 (1960), **83,** 1617 (1961); Seyferth, Heeren, Singh, Grim, and Hughes, *J. Organometal. Chem.* **5,** 267 (1966).

[157] Corey, McCormick, and Swensen, *J. Am. Chem. Soc.* **86,** 1884 (1964).

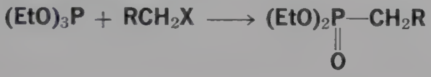
[158] Wittig and Schöllkopf, *Chem. Ber.* **87,** 1318 (1954).

[159] For example, see Johnson and LaCount, *Tetrahedron* **9,** 130 (1960); Bestmann and Kratzer, *Chem. Ber.* **95,** 1894 (1962).



$$(RO)_2\underset{\underset{O}{\|}}{P}-\underset{\underset{R'}{|}}{CH}-R'' \xrightarrow{\text{base}} (RO)_2\underset{\underset{O}{\|}}{P}-\underset{\underset{R'}{|}}{\overset{\ominus}{\bar{C}}}-R'' \xrightarrow{\overset{|}{-C=O}} -\underset{|}{C}=\underset{\underset{R'}{|}}{C}-R'' + (RO)_2PO_2^-$$

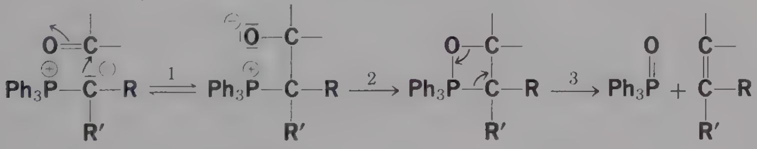
This method, sometimes called the *Horner reaction,* has several advantages over the use of phosphoranes. These ylides are more reactive than the corresponding phosphoranes, and when R′ is an electron-withdrawing group, these compounds often react with ketones which are inert to phosphoranes. In addition, the phosphorus product is a phosphate ester and hence soluble in water, unlike Ph_3PO, which makes it easy to separate it from the olefin product. Phosphonates are also cheaper than phosphonium salts and may easily be prepared by the *Arbuzov reaction:*[161]



$$(EtO)_3P + RCH_2X \longrightarrow (EtO)_2\underset{\underset{O}{\|}}{P}-CH_2R$$

Ylides formed from $Ar_2\underset{\underset{O}{\|}}{P}CHRR'$ and $(Me_2N)_3\overset{\oplus}{P}CHRR'$[162] share some of these advantages.

The mechanism of the key step of the Wittig reaction consists of at least two and perhaps three steps:



Betaine

Step 1 may or may not be an equilibrium reaction. Steps 2 and 3 constitute an elimination of Ph_3PO (see reaction **7-20,** p. 769), and may be simultaneous. Either step 1 or steps 2–3 may be rate-determining. Step 1 has been shown to be reversible for stable ylides (those containing COR, CN, etc., groups), by the preparation in another way of the betaine, and the demonstration that the ylide may be prepared from it.[163] Step 1 has also been shown to be reversible for at least one unstable ylide.[164] According to this mechanism, an optically active phosphonium salt ($RR'R''\overset{\oplus}{P}CHR_2$) should retain its configuration all the way through the reaction, and it should be preserved in the phosphine oxide: $RR'R''PO$. This has been shown to be the case.[165]

---

[160] Horner, Hoffman, and Wippel, *Chem. Ber.* **91,** 61 (1958).

[161] For a review of the Arbuzov reaction, see Arbuzov, *Pure Appl. Chem.* **9,** 307–335 (1964).

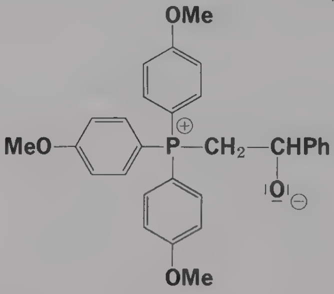
[162] Oediger and Eiter, *Ann.* **682,** 58 (1965).

[163] Speziale and Bissing, *J. Am. Chem. Soc.* **85,** 3878 (1963).

[164] Schlosser and Christmann, *Angew. Chem. Intern. Ed. Engl.* **4,** 689 (1965).

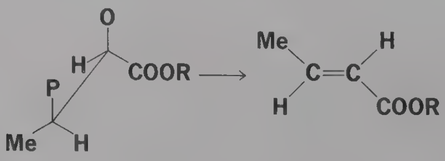
[165] McEwen, Kumli, Blade-Font, Zanger, and VanderWerf, *J. Am. Chem. Soc.* **86,** 2378 (1964).

We may examine the question of when step 1 is faster than steps 2–3, and vice versa. We have already seen that the ylide is increased in stability (and decreased in reactivity) by the presence of electron-withdrawing groups on the carbon. Another factor is the presence of electron-donating groups on the phosphorus. These groups stabilize the ylide canonical form (of the resonance hybrid) at the expense of the C=P form by decreasing the positive charge on the phosphorus. This increases the reactivity of the ylide and explains, for example, why trialkyl phosphorus ylides are more reactive than the triaryl variety. On the other hand, once the betaine is formed, these factors work in precisely the opposite direction. Electron-withdrawing groups on the carbon increase the reactivity of the betaine, because they stabilize (by conjugation) the newly forming double bond; and electron-donating substituents on the phosphorus decrease the reactivity of the betaine, since they decrease the positive charge on the phosphorus and make it less attractive to the negative oxygen. We see from all this that, with ylides containing electron-donating groups on the phosphorus, the first step will be faster than the subsequent ones. In some cases, indeed, it has proved possible to isolate the betaine, an example being **41**.[166] However, if there are electron-withdrawing groups on the carbon, then the first step will be slower than the subsequent ones, and it should be much more difficult to isolate the betaine. Up to now, no such betaine has been isolated. As expected, reversibility of step 1 is most important when the betaine is stable.



41

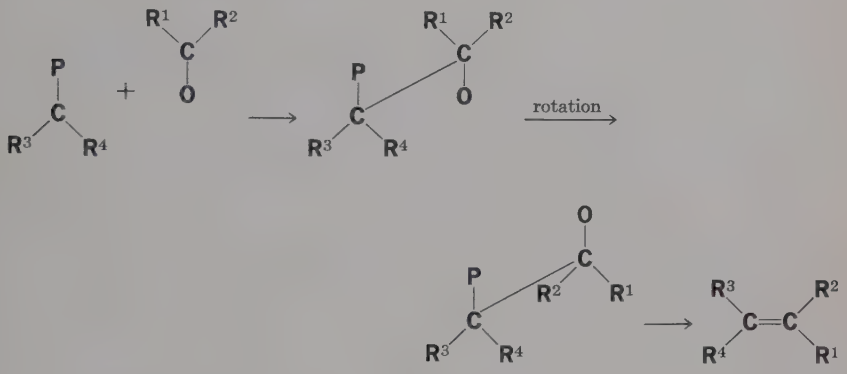
These considerations make possible at least some conclusions about the stereochemistry of the reaction. If the betaine has two asymmetric carbons, there are two diastereomeric DL pairs. In those cases where betaine formation is reversible, the thermodynamically more stable diastereomer will be predominantly formed before elimination (a cis process, in this case) occurs, and this diastereomer will normally give the trans olefin:

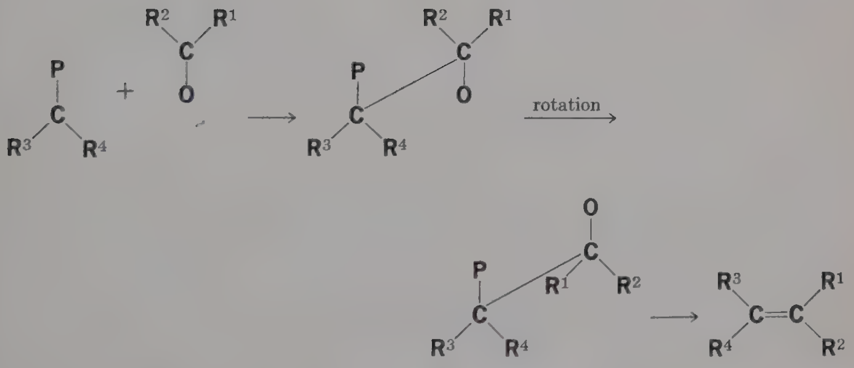


---

[166] Wittig, Weigmann, and Schlosser, *Chem. Ber.* **94**, 676 (1961).

In the case of betaine formation which is irreversible, or where the reversibility is not important, which diastereomer forms is determined by the way the ylide and carbonyl compound line up. Once the betaine is formed, the stereochemistry of the olefin is determined by the fact that elimination is cis. The two possibilities can be shown:



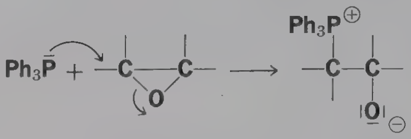


From this discussion it may be predicted that ylides formed from triphenylphosphine and ordinary aldehydes or ketones should give cis or mixtures of cis and trans olefins, but that ylides formed from trialkylphosphines or from aldehydes or ketones containing stabilizing groups should give trans olefins. This generalization is largely borne out.[167] The cis-trans ratio may also be changed by changes in solvent. It has been found possible to control the reaction so that either the cis or the trans olefin is the main product.[168]

[167] See, for example, Ketcham, Jambotkar, and Martinelli, *J. Org. Chem.* **27**, 4666 (1962); House and Rasmusson, *J. Org. Chem.* **26**, 4278 (1961); Bestmann and Kratzer, ref. 159; Kucherov, Kovalev, Nazarova, and Yanovskaya, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1960**, 1405; and Yanovskaya and Kucherov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964**, 1252.

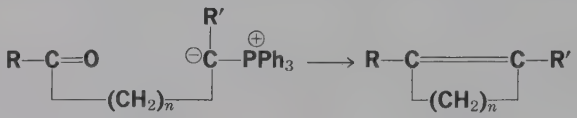
[168] For reviews of the stereochemistry, see Bergelson and Shemyakin, *Angew. Chem. Intern. Ed. Engl.* **3**, 250–260 (1964), *Pure Appl. Chem.* **9**, 271–283 (1964). Also see Bergelson and Shemyakin, *Tetrahedron* **19**, 149 (1963); House, Jones, and Frank, *J. Org. Chem.* **29**, 3327 (1964); Wadsworth, Schupp, Seus, and Ford, *J. Org. Chem.* **30**, 680 (1965).

The betaine may be formed in a completely different manner, by nucleophilic substitution by a phosphine on an epoxide (reaction **0-49**, p. 334):

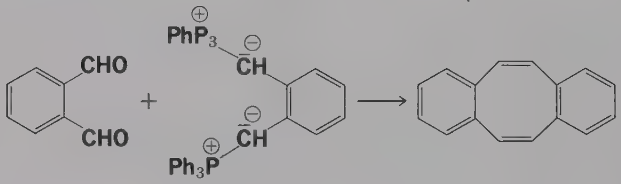


The betaine formed in this way, of course, may then be converted to the olefin.

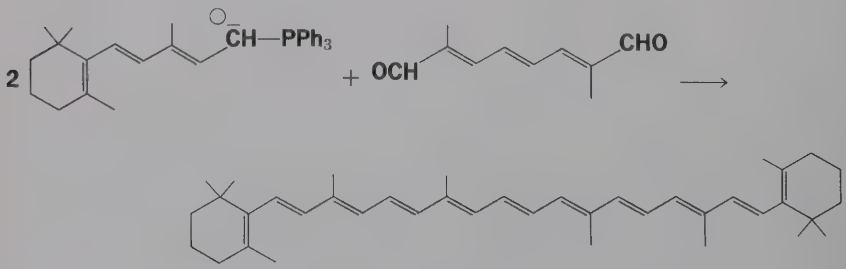
The Wittig reaction has been carried out intramolecularly, to prepare rings containing from 5 to 16 carbons,[169] both by single ring closure:



and double ring closure:



The Wittig reaction has proved very useful in the synthesis of natural products, some of which are quite difficult to prepare in other ways. One example out of many is the synthesis of β-carotene:[170]



β-Carotene

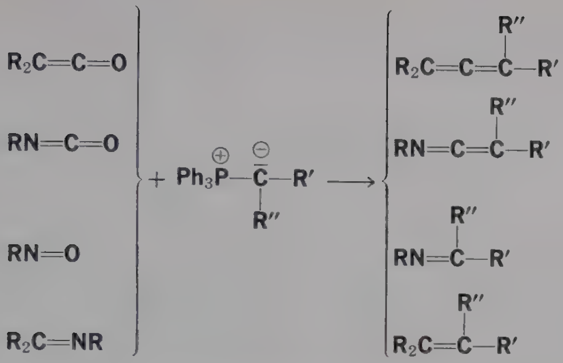
Phosphorus ylides also react in a similar manner with the C=O bonds of ketenes and isocyanates, the N=O of nitroso groups, and the C=N of imines:[171]

---

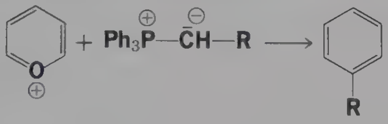
[169] See, for example, Wittig, Eggers, and Duffner, *Ann.* **619,** 10 (1958); Griffin and Witschard, *J. Org. Chem.* **27,** 3334 (1962), **29,** 1001 (1964); Griffin and Peters, *J. Org. Chem.* **28,** 1715 (1963); Schweizer, *J. Am. Chem. Soc.* **86,** 2744 (1964).

[170] Wittig and Pommer, German patent 954,247 (1956), *CA* **53,** 2279 (1959).

[171] Bestmann and Seng, *Tetrahedron* **21,** 1373 (1965).

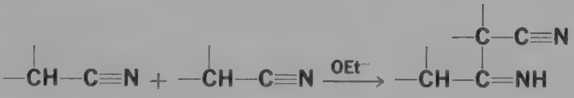


Pyrylium salts react with ylides in the following manner:[172]

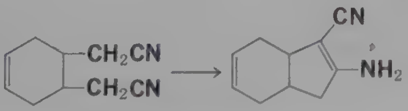


OS **40,** 36, 66, 85; **45,** 33, 44.

6-46 The Thorpe reaction



In the *Thorpe reaction,* the α-carbon of one nitrile molecule is added to the CN carbon of another, so that this reaction is analogous to the aldol condensation (**6-39**). The C=NH bond is, of course, hydrolyzable (reaction **6-2**), so that β-keto nitriles may be prepared in this manner. The Thorpe reaction may be done internally, in which case it is called the *Thorpe-Ziegler reaction.*[173] This is a useful method for closing large rings. Yields are high for five- to eight-membered rings, fall off to about zero for rings of 9 to 13 members, but are high again for 14-membered and larger rings, if high-dilution techniques are employed. The product in the Thorpe-Ziegler reaction is not the imine, but the tautomeric enamine, e.g.:



Other active compounds may also be added to nitriles. In particular, CF_3CN adds compounds ZCH_2Z, in a Knoevenagel-type reaction.[174]

---

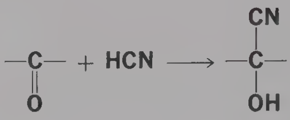
[172] Märkl, *Angew. Chem. Intern. Ed. Engl.* **1,** 511 (1962).

[173] For a review, see Schaefer and Bloomfield, *Org. Reactions* **15,** 1-203 (1967).

[174] Josey, *J. Org. Chem.* **29,** 707 (1964).

J. Other carbon nucleophiles

6-47 The formation of cyanohydrins



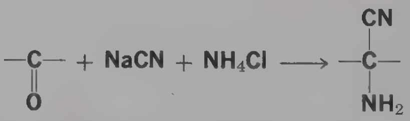
$$-\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}- + \mathrm{HCN} \longrightarrow -\overset{\mathrm{CN}}{\underset{\mathrm{OH}}{\mathrm{C}}}-$$

The addition of HCN to aldehydes or ketones produces cyanohydrins.[175] This is an equilibrium reaction. For aldehydes and aliphatic ketones the equilibrium lies to the right; therefore the reaction is quite feasible. However, ketones ArCOR give poor yields, and the reaction cannot be carried out with ArCOAr, since the equilibrium is too far to the left. With aromatic aldehydes the benzoin condensation (reaction **6-53**) competes. With α,β-unsaturated aldehydes and ketones, 1,4 addition competes (reaction **5-20,** p. 610). Frequently it is the bisulfite addition product which is treated with CN^-, in which case the reaction is actually nucleophilic substitution. This method is especially useful for aromatic aldehydes, since it avoids competition from the benzoin condensation. If desired, it is possible to hydrolyze the cyanohydrin *in situ,* without its isolation, to the corresponding α-hydroxy acid. This reaction is important in the *Kiliani method* of extending the carbon chain of a sugar.

The addition is nucleophilic, and the actual nucleophile is CN^-, so that the reaction rate is increased by the addition of base. This was demonstrated by Lapworth in 1903, and consequently this was one of the first organic mechanisms to be known.[176]

OS **I,** 336; **II,** 7, 29, 387; **III,** 436; **IV,** 58, 506. For the reverse reaction, see OS **III,** 101.

6-48 The Strecker synthesis



$$-\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}- + \mathrm{NaCN} + \mathrm{NH_4Cl} \longrightarrow -\overset{\mathrm{CN}}{\underset{\mathrm{NH_2}}{\mathrm{C}}}-$$

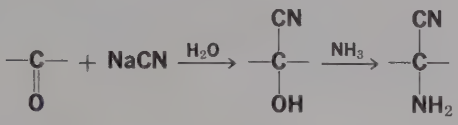
α-Amino nitriles may be prepared in one step by the treatment of an aldehyde or ketone with NaCN and NH_4Cl. This is called the *Strecker synthesis;* it is actually a special case of the Mannich reaction (**6-17**). Since the CN is easily hydrolyzed to the acid, this is a convenient method for the preparation of α-amino acids. The reaction has also been carried out with NH_3 + HCN, and with NH_4CN. Salts of primary and secondary amines may be used instead of NH_4^+, to obtain N-substituted and N,N-disubstituted α-amino nitriles. When *formaldehyde* is treated with NaCN and the salt of an amine, the reaction is known as *cyanomethylation* of the amine. Unlike reaction **6-47,** the Strecker synthesis is useful for aromatic as well as aliphatic ketones.

---

[175] For a review, see Mowry, *Chem. Rev.* **42,** 189–283 (1948), pp. 231–240.

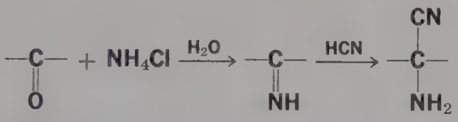
[176] Lapworth, *J. Chem. Soc.* **83,** 998 (1903).

There are two possible pathways for the reaction. The cyanohydrin may be produced first, and a nucleophilic substitution (reaction **0-46,** p. 332) may then follow:



$$\underset{\overset{\|}{\text{O}}}{-\text{C}-} + \text{NaCN} \xrightarrow{H_2O} \overset{\text{CN}}{\underset{\text{OH}}{-\text{C}-}} \xrightarrow{NH_3} \overset{\text{CN}}{\underset{\text{NH}_2}{-\text{C}-}}$$

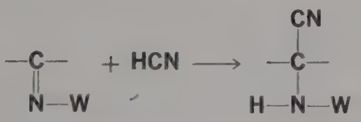
or ammonia (or the amine) may add first to give an imine (reaction **6-14**), to which NaCN adds (reaction **6-49**):



$$\underset{\overset{\|}{\text{O}}}{-\text{C}-} + \text{NH}_4\text{Cl} \xrightarrow{H_2O} \underset{\overset{\|}{\text{NH}}}{-\text{C}-} \xrightarrow{HCN} \overset{\text{CN}}{\underset{\text{NH}_2}{-\text{C}-}}$$

OS **I,** 21, 355; **III,** 66, 84, 88, 275; **IV,** 274; **43,** 25.

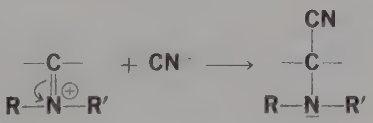
6-49 The addition of HCN to the C=N bond



$$\underset{\overset{\|}{\text{N}-\text{W}}}{-\text{C}-} + \text{HCN} \longrightarrow \overset{\text{CN}}{\underset{\text{H}-\text{N}-\text{W}}{-\text{C}-}}$$

W = H, R, Ar, OH, NHAr, etc.

HCN adds to imines, Schiff bases, hydrazones, oximes, and similar compounds. CN^- may be added to iminium ions:



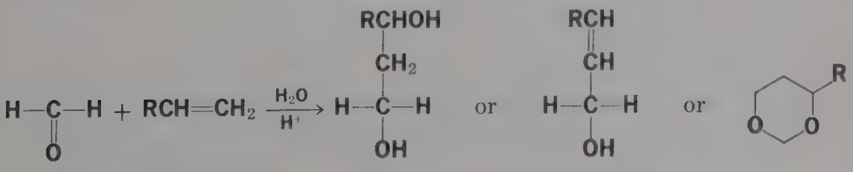
$$\underset{\overset{\|}{\text{R}-\overset{\oplus}{\text{N}}-\text{R}'}}{-\text{C}-} + \text{CN}^- \longrightarrow \overset{\text{CN}}{\underset{\text{R}-\text{N}-\text{R}'}{-\text{C}-}}$$

There are no *Organic Syntheses* references, but see OS **42,** 30, for a related reaction.

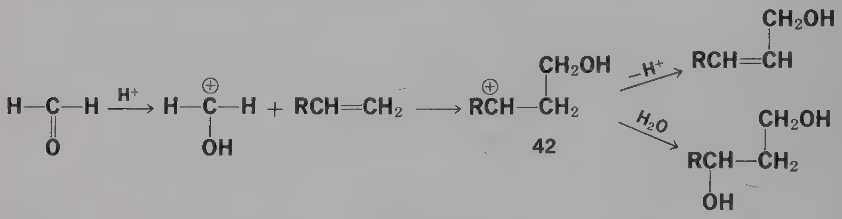
6-50 Addition of ArH to C=O, C=N, and C≡N bonds.

These reactions are discussed under aromatic substitution: **1-15** (p. 416), **1-17** (p. 417), and **1-23** to **1-28** (pp. 420–425).

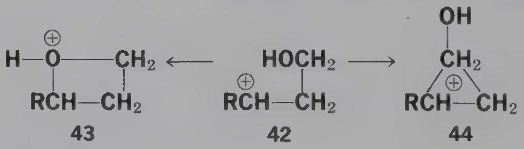
6-51 The Prins reaction



The addition of an olefin to formaldehyde in the presence of an acid catalyst is called the *Prins reaction*.[177] There are three main products possible, and which one predominates depends on the olefin and the conditions. When the product is the 1,3-diol or the dioxane, the reaction involves addition to the C=C as well as to the C=O. The mechanism is one of electrophilic attack, on both double bonds. The acid first protonates the C=O, and the resulting carbonium ion attacks the C=C:



42 may undergo loss of H^+ to give the olefin or may add water to give the diol. It has been proposed that **42** is stabilized by neighboring-group attraction, with either the oxygen[178] or a carbon[179] stabilizing the charge (**43** and **44**, respectively). This stabilization is postulated to explain the fact



that with cyclohexenes, the addition is trans. A backside attack of H_2O on the three- or four-membered ring would account for it. Other products are obtained too, which can be explained on the basis of **43** or **44**.[178,179] However, when the reaction was run with *cis*- and *trans*-4-octene, it was only partly stereospecific, so **42** here cannot be completely cyclic.[180] Also, with β-bromostyrene, the addition was stereospecific and cis.[181] Since addition to the C=C bond is electrophilic, Markovnikov's rule is followed. The dioxane product may arise from a reaction between the 1,3-diol and formaldehyde (reaction **6-6**) or between **42** and formaldehyde, or even between the olefin and a formaldehyde dimer: $HOCH_2OCH_2^+$.[182]

Lewis acids such as $SnCl_4$ also catalyze the reaction, in which case the species which adds to the olefin is $H_2\overset{\oplus}{C}—O—\overset{\ominus}{Sn}Cl_4$.[183] The reaction can also be catalyzed by peroxides, in which case the mechanism is probably a free-radical one.

---

[177] For reviews, see Arundale and Mikeska, *Chem. Rev.* **51**, 505 (1952); and Roberts, in Olah, "Friedel-Crafts and Related Reactions," vol. 2, pp. 1175–1210, Interscience Publishers, Inc., New York, 1963.

[178] Blomquist and Wolinsky, *J. Am. Chem. Soc.* **79**, 6025 (1957).

[179] Dolby, Lieske, Rosencrantz, and Schwarz, *J. Am. Chem. Soc.* **85**, 47 (1963); Dolby and Schwarz, *J. Org. Chem.* **28**, 1456 (1963).

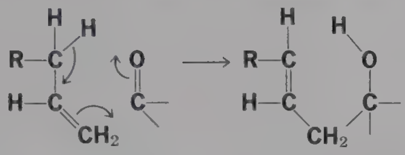
[180] LeBel, Liesemer, and Mehmedbasich, *J. Org. Chem.* **28**, 615 (1963); Portoghese and Smissman, *J. Org. Chem.* **27**, 719 (1962).

[181] Bernardi and Leone, *Tetrahedron Letters* **1964**, 499.

[182] Smissman, Schnettler, and Portoghese, *J. Org. Chem.* **30**, 797 (1965).

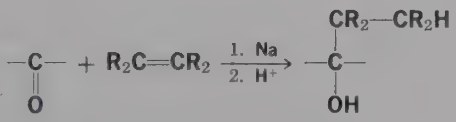
[183] Yang, Yang, and Ross, *J. Am. Chem. Soc.* **81**, 133 (1959).

The reaction has been performed with other aldehydes and even with ketones; without a catalyst, but with heat.[184] The aldehydes and ketones here are active ones, such as chloral and acetoacetic ester. The product in these cases is a β-hydroxy olefin, and a cyclic mechanism has been postulated:



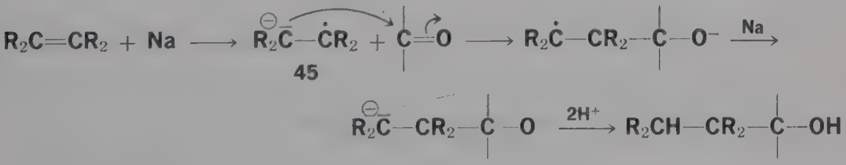
This reaction is reversible, and suitable β-hydroxy olefins may be cleaved by heat (reaction **7-35**, p. 779). There is evidence that the cleavage reaction occurs by a cyclic mechanism (p. 779), and, by the principle of microscopic reversibility, the addition mechanism should be cyclic too. Note that this reaction is an oxygen analog of the ene synthesis (p. 603).

There is still another way in which olefins may be added to the C═O bond. If the two compounds are treated with sodium, there is addition accompanied by reduction:[185]



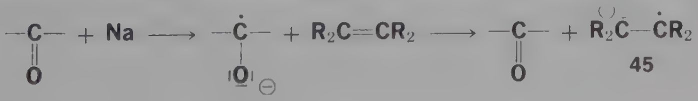
$$\underset{\underset{\displaystyle O}{\|}}{-C-} + R_2C{=}CR_2 \xrightarrow[2.\ H^+]{1.\ Na} \overset{\overset{\displaystyle CR_2{-}CR_2H}{|}}{\underset{\underset{\displaystyle OH}{|}}{-C-}}$$

The mechanism probably involves an ion-radical:



$$R_2C{=}CR_2 + Na \longrightarrow \underset{\displaystyle 45}{R_2\overset{\ominus}{\bar{C}}{-}\dot{C}R_2} + \overset{|}{\underset{|}{C}}{=}O \longrightarrow R_2\dot{C}{-}CR_2{-}\overset{|}{\underset{|}{C}}{-}O^- \xrightarrow{Na} R_2\overset{\ominus}{\bar{C}}{-}CR_2{-}\overset{|}{\underset{|}{C}}{-}O \xrightarrow{2H^+} R_2CH{-}CR_2{-}\overset{|}{\underset{|}{C}}{-}OH$$

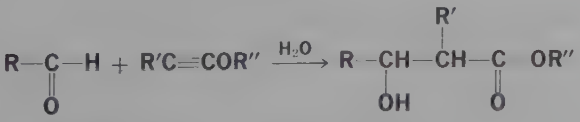
Alternatively, **45** might be formed indirectly, from an initially formed ketyl:



$$\underset{\underset{\displaystyle O}{\|}}{-C-} + Na \longrightarrow \underset{\underset{\displaystyle |\underline{O}|^{\ominus}}{|}}{-\dot{C}-} + R_2C{=}CR_2 \longrightarrow \underset{\underset{\displaystyle O}{\|}}{-C-} + \underset{\displaystyle 45}{R_2\bar{C}{-}\dot{C}R_2}$$

OS **IV**, 786.

6-52 The addition of triple-bond compounds



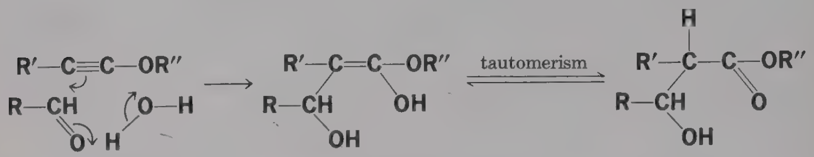
$$R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}H + R'C{\equiv}COR'' \xrightarrow{H_2O} R{-}\underset{\underset{\displaystyle OH}{|}}{CH}{-}\overset{\overset{\displaystyle R'}{|}}{CH}{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OR''$$

---

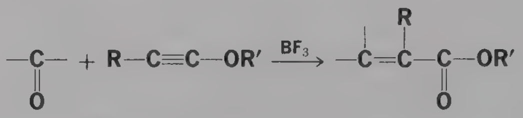
[184] Arnold and Veeravagu, *J. Am. Chem. Soc.* **82**, 5411 (1960).

[185] Kochi, *J. Org. Chem.* **28**, 1960, 1969 (1963).

Aldehydes and water may be added to alkynyl ethers to give β-hydroxy esters.[186] The reaction is applicable to aldehydes only, but the yields rapidly diminish with chain length.[187] Formaldehyde is most commonly used. A cyclic mechanism has been suggested:

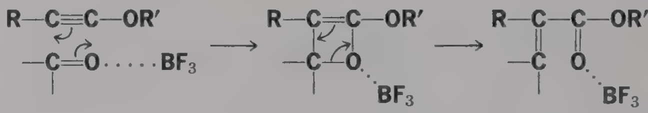


If the alkynyl ether is treated with a carbonyl compound, in the absence of water but in the presence of BF_3, an α,β-unsaturated ester is produced:[188]

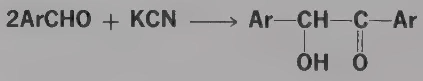


$$\underset{\mathrm{O}}{\overset{}{-\underset{\|}{\mathrm{C}}-}} + \mathrm{R{-}C{\equiv}C{-}OR'} \xrightarrow{\mathrm{BF_3}} -\overset{|}{\mathrm{C}}{=}\overset{\mathrm{R}}{\overset{|}{\mathrm{C}}}-\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-\mathrm{OR'}$$

This reaction is much more general, and the carbonyl compound may be an aldehyde, ketone, ester, or amide. A cyclic mechanism has also been proposed in this case:



6-53 The benzoin condensation



$$2\mathrm{ArCHO} + \mathrm{KCN} \longrightarrow \mathrm{Ar}-\underset{\mathrm{OH}}{\underset{|}{\mathrm{CH}}}-\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-\mathrm{Ar}$$

When certain aldehydes are treated with cyanide ion, *benzoins* are produced, in a reaction called the *benzoin condensation.* The condensation may be regarded as involving the addition of one molecule of aldehyde to the C=O group of another. The reaction can be accomplished only for aromatic aldehydes, though not for all of them,[189] and for glyoxals: RCOCHO. The two molecules of aldehyde obviously perform different functions. The one which no longer has a C—H bond in the product is called the *donor,* because it has "donated" its hydrogen to the oxygen of the other molecule, the *acceptor.* Some aldehydes can perform only one of these functions and hence cannot be self-condensed, though they can often be condensed with a different aldehyde. For example, *p*-dimethylaminobenzaldehyde is not an acceptor, but only a donor. Thus it cannot condense with itself, but it can condense with benzaldehyde, which can perform both functions, but which is a better acceptor than it is a donor.

---

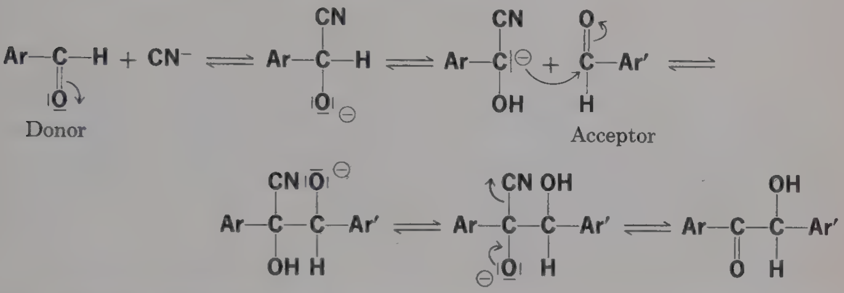
[186] For a review, see Arens, *Advan. Org. Chem.* **2,** 117–212 (1960), pp. 174–178.

[187] Vieregge and Arens, *Rec. trav. chim.* **78,** 921 (1959).

[188] Vieregge, Bos, and Arens, *Rec. trav. chim.* **78,** 664 (1959); Krasnaya and Kucherov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1962,** 990; Bos and Arens, *Rec. trav. chim.* **83,** 845 (1963).

[189] For a review, see Ide and Buck, *Org. Reactions* **4,** 269–304 (1948).

The following is the accepted mechanism:



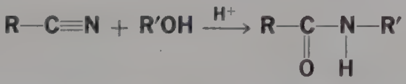
The reaction is reversible. The key step of the reaction, the loss of the aldehydic proton, can take place because the acidity of this C—H bond is increased by the electron-withdrawing power of the CN group.

OS **I,** 94.

Reactions in Which Carbon Adds to the Hetero Atom

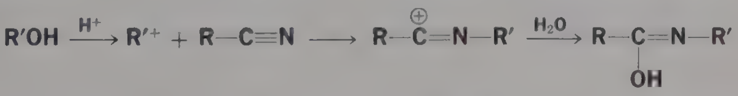
A. Oxygen adding to the carbon

6-54 The Ritter reaction



$$R{-}C{\equiv}N + R'OH \xrightarrow{H^+} R{-}\underset{\overset{\|}{O}}{C}{-}\underset{\overset{|}{H}}{N}{-}R'$$

Alcohols may be added to nitriles in an entirely different manner from that of reaction **6-10.** In this reaction, the alcohol is converted by a strong acid to the carbonium ion, which adds to the negative nitrogen, water adding to the carbon:



$$R'OH \xrightarrow{H^+} R'^+ + R{-}C{\equiv}N \longrightarrow R{-}\overset{\oplus}{C}{=}N{-}R' \xrightarrow{H_2O} R{-}\underset{\underset{OH}{|}}{C}{=}N{-}R'$$

The immediate product tautomerizes to the N-alkyl amide. Only fairly stable carbonium ions react: secondary, tertiary, benzylic, etc.—primary alcohols do not give the reaction. The carbonium ion need not be generated from an alcohol but may come from protonation of an olefin or from other sources, among them RCOOH + concentrated $H_2SO_4 \longrightarrow R^+$ (R in this case, tertiary only).[190] In any case, the reaction is called the *Ritter reaction.*[191] HCN also gives the reaction, the product being a formamide.

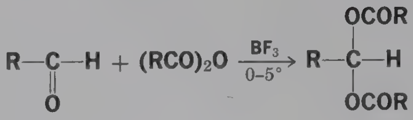
OS **42,** 16; **44,** 44.

---

[190] Haaf, *Chem. Ber.* **96,** 3359 (1963).

[191] For a review, see Zil'berman, *Russ. Chem. Rev.* **29,** 331–344 (1960), pp. 334–337.

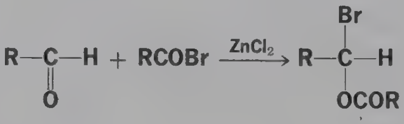
6-55 Acylation of aldehydes and ketones



$$\mathrm{R{-}\underset{\overset{\|}{O}}{C}{-}H + (RCO)_2O \xrightarrow[0\text{–}5^\circ]{BF_3} R{-}\overset{OCOR}{\underset{OCOR}{C}}{-}H}$$

An acylal

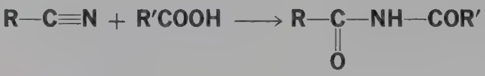
Aldehydes only can be converted to acylals by treatment with an anhydride in the presence of BF_3. In a similar reaction, aldehydes and some ketones (though not acetone) add the elements of an acyl bromide, when treated with the acyl bromide and $ZnCl_2$:[192]



$$\mathrm{R{-}\underset{\overset{\|}{O}}{C}{-}H + RCOBr \xrightarrow{ZnCl_2} R{-}\overset{Br}{\underset{OCOR}{C}}{-}H}$$

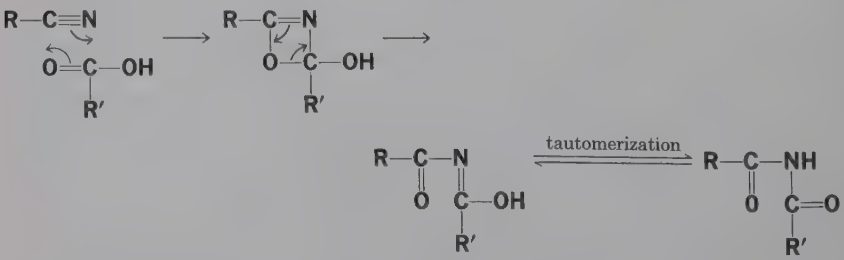
OS **IV,** 489.

6-56 The addition of acids to nitriles



$$\mathrm{R{-}C{\equiv}N + R'COOH \longrightarrow R{-}\underset{\overset{\|}{O}}{C}{-}NH{-}COR'}$$

Imides are the principal products when carboxylic acids are added to nitriles.[193] Several mechanisms have been proposed which more or less fit the data. In one of them the nitrogen is attacked directly by the carboxyl carbon, and in another the OH of the acid attacks the nitrile carbon, and a migration of the acyl group follows. A more recently proposed mechanism is similar to the one proposed for reaction **6-52:**[194]



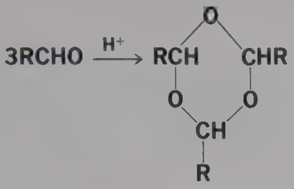
---

[192] Euranto and Kujanpää, *Acta Chem. Scand.* **15,** 1209 (1961).

[193] For a review, see Ref. 191, pp. 340–341.

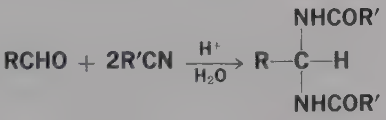
[194] Durrell, Young, and Dresdner, *J. Org. Chem.* **28,** 831 (1963).

6-57 The addition of aldehydes to aldehydes



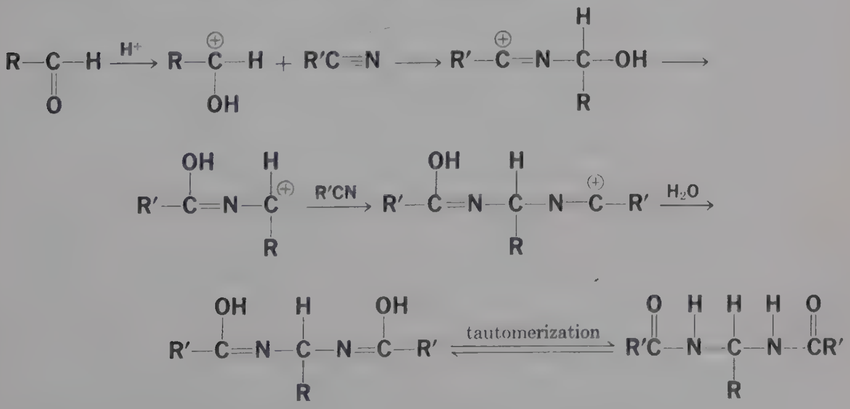
When catalyzed by acids, low-molecular-weight aldehydes add to each other to give cyclic acetals, the most common product being the trimer.[195] The cyclic trimer of formaldehyde is called *trioxane,* and that of acetaldehyde is known as *paraldehyde.* Under certain conditions, it is possible to get tetramers[196] or dimers. Aldehydes can also polymerize to linear polymers, but here a small amount of water is required to form hemiacetal groups at the ends of the chains. Since trimers and polymers of aldehydes are acetals, they are stable to bases but may be hydrolyzed by acids. Because formaldehyde and acetaldehyde have low boiling points, it is often convenient to use them in the form of their trimers or polymers.

6-58 The addition of aldehydes to nitriles



$$\mathrm{RCHO} + 2\mathrm{R'CN} \xrightarrow[\mathrm{H_2O}]{\mathrm{H^+}} \mathrm{R{-}}\overset{\mathrm{NHCOR'}}{\underset{\mathrm{NHCOR'}}{\mathrm{C}}}\mathrm{{-}H}$$

In the presence of acids, two moles of a nitrile add to one of aldehyde to give *amidals.*[197] The reaction is applicable only to aldehydes which do not contain an α hydrogen. Apparently the mechanism is as follows:



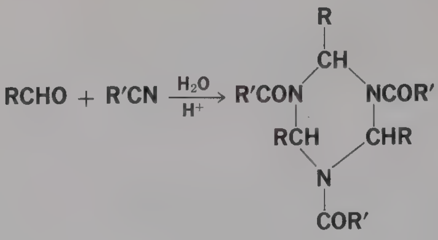
---

[195] For a review, see Bevington, *Quart. Rev.* (*London*) **6,** 141–156 (1952).

[196] Barón, *Nature* **192,** 258 (1961); Barón, Manderola, and Westerkamp, *Can. J. Chem.* **41,** 1893 (1963).

[197] For a review, see Ref. 191, pp. 333–334.

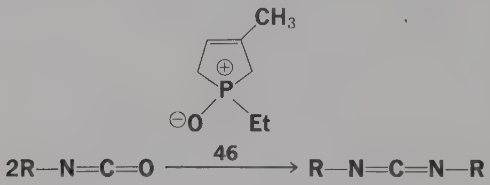
Nitriles can also condense cyclically with aldehydes:



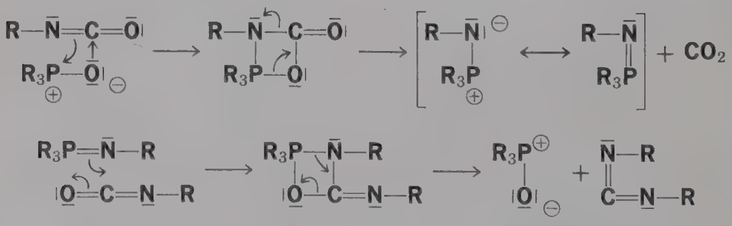
OS **IV**, 518.

B. Nitrogen adding to the carbon

6-59 The addition of isocyanates to isocyanates



The treatment of isocyanates with 3-methyl-1-ethyl-3-phospholene-1-oxide (**46**) represents a useful method for the synthesis of carbodiimides in good yields.[198] The mechanism does not simply involve the addition of one mole of isocyanate to another, since the kinetics are first order in isocyanate and first order in catalyst. The following mechanism has been proposed (the catalyst is here represented as $R_3\overset{\oplus}{P}-\overset{\ominus}{O}$):[199]

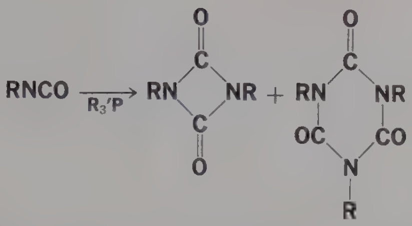


The first two steps together are rate-determining. According to this mechanism, one molecule of isocyanate undergoes addition to C=O and the other, addition to C=N. When isocyanates are treated with phosphines (instead of phosphine oxides, as above), there is simple addition to give cyclic dimers and trimers:

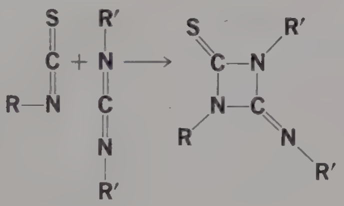
---

[198] Campbell, Monagle, and Foldi, *J. Am. Chem. Soc.* **84,** 3673 (1962).

[199] Monagle, Campbell, and McShane, *J. Am. Chem. Soc.* **84,** 4288 (1962).



A number of other compounds also catalyze this cyclization. Isothiocyanates carrying electron-withdrawing substituents add to carbodiimides to give four-membered-ring compounds:[200]

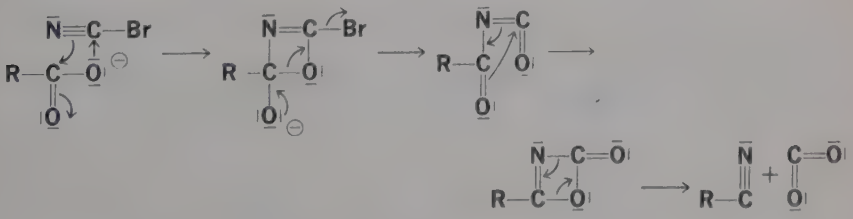


OS **43,** 31.

6-60 The conversion of acid salts to nitriles

$$\mathrm{RCOO^- + BrCN \xrightarrow{250\text{–}300°} RCN + CO_2}$$

Salts of aliphatic or aromatic acids may be converted to the corresponding nitriles by heating with BrCN or ClCN. Despite appearances, this is not a substitution reaction. When $R^{14}COO^-$ was used, the label appeared in the nitrile and not in the CO_2,[201] and optical activity in R is retained.[202] The acyl isocyanate RCON=C=O could be isolated from the reaction mixture; hence the following mechanism was proposed:[201]



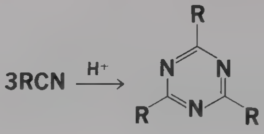
---

[200] Ulrich and Sayigh, *Angew. Chem. Intern. Ed. Engl.* **4,** 520 (1965).

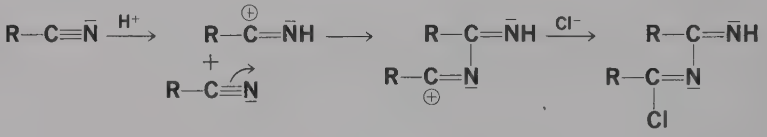
[201] Douglas, Eccles, and Almond, *Can. J. Chem.* **31,** 1127 (1953); Douglas and Burditt, *Can. J. Chem.* **36,** 1256 (1958).

[202] Barltrop, Day, and Bigley, *J. Chem. Soc.* **1961,** 3185.

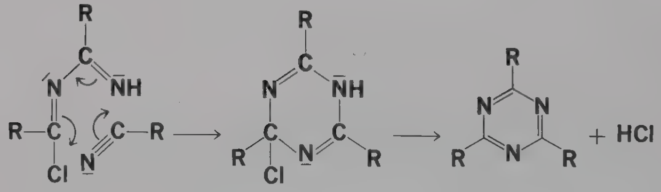
6-61 The trimerization of nitriles



Nitriles may be trimerized with various acids, bases, or other catalysts. HCl is most often used, and then the reaction is similar to reaction **6-57.** However, most nitriles with an α hydrogen do not give the reaction. Mixed triazines can be obtained from mixtures of nitriles.[203] The mechanism with HCl may be as follows:[203]



46



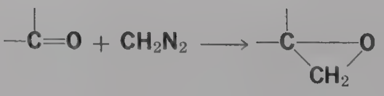
Intermediates of the type **46** have been isolated.

Aromatic nitriles, but not aliphatic ones, may be trimerized without a catalyst, upon heating to 350 to 500° at pressures of 35,000 to 50,000 atm.[204]

OS **III,** 71.

C. Carbon adding to the carbon. The reactions in this group (**6-62** to **6-66**) are cycloadditions.

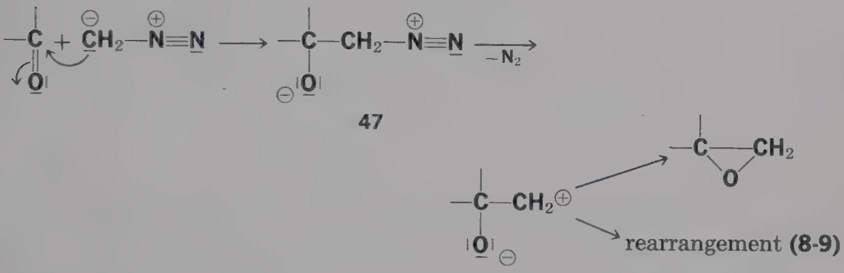
6-62 The formation of epoxides from aldehydes and ketones



---

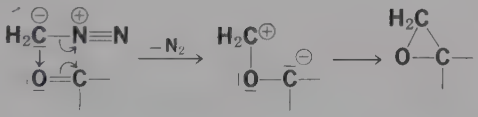
[203] Grundmann, Weisse, and Seide, *Ann.* **577,** 77 (1952); Grundmann, *Chem. Ber.* **97,** 3262 (1964).
[204] Bengelsdorf, *J. Org. Chem.* **28,** 1369 (1963).

When an aldehyde or ketone is treated with diazomethane, CH_2 is added to the C=O bond to give an epoxide.[205] This reaction is similar in appearance to reaction **5-37** (p. 643) but does not usually involve a free carbene intermediate. An important side reaction is the formation of an aldehyde or ketone with one more carbon than the starting compound (reaction **8-9,** p. 810). The reaction may be carried out with many aldehydes, ketones, and quinones. Diazomethane is the most common diazoalkane used, but others have also been employed. A mechanism that accounts for both reactions is

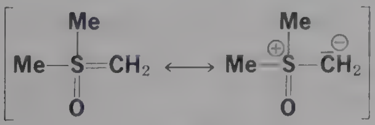


47

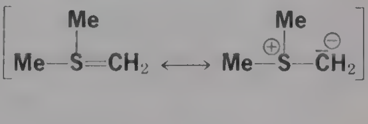
Compound **47** or nitrogen-containing derivatives of it have sometimes been isolated. The last two steps leading to the epoxide (S_N) may be concerted. It is also possible that another pathway exists,[206] which can lead only to the epoxide:



The sulfur ylides dimethyloxosulfonium methylide (**48**) and dimethylsulfonium methylide (**49**) may be used instead of diazo compounds. These re-



48



49

agents are much more specific for epoxide formation, giving few side reactions.[207] Addition of **48** and **49** to dihydrotestosterone gave epoxides of opposite stereochemistry:[208]

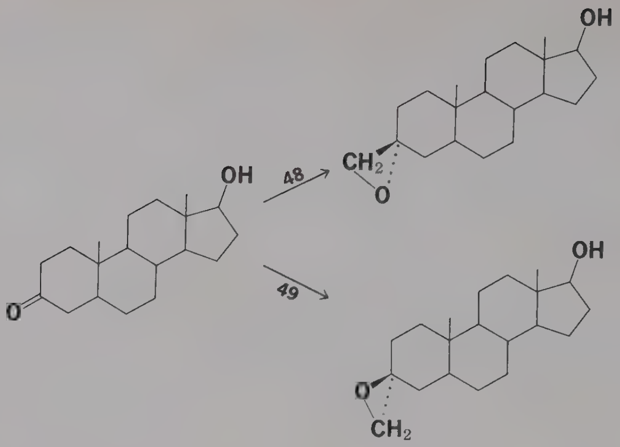
---

[205] For reviews, see Gutsche, *Org. Reactions* **8,** 364–429 (1964); and Eistert, "Newer Methods of Preparative Organic Chemistry," vol. 1, pp. 521–537, Interscience Publishers, Inc., New York, 1948.

[206] Bradley, Cowell, and Ledwith, *J. Chem. Soc.* **1964,** 4334.

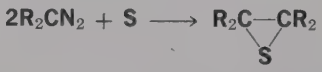
[207] Corey and Chaykovsky, *J. Am. Chem. Soc.* **87,** 1353 (1965).

[208] Cook, Corley, and Wall, *Tetrahedron Letters* **1965,** 891.



Phosphorus ylides do not give the reaction, but give reaction **6-45** instead. Also see reaction **6-43.**

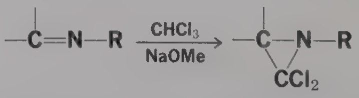
6-63 The formation of episulfides



$$2R_2CN_2 + S \longrightarrow R_2C\overset{\displaystyle S}{\text{—}}CR_2$$

Diazoalkanes, treated with sulfur, give episulfides.[209] It is likely that $R_2C{=}S$ is an intermediate, which is attacked by another molecule of diazoalkane, in a process similar to reaction **6-62.** Thioaldehydes and thiones *do* react with diazoalkanes to give episulfides. As in **6-62,** sulfur ylides may also be employed.[207]

6-64 The formation of aziridines



$$-\overset{|}{C}{=}N{-}R \xrightarrow[\text{NaOMe}]{\text{CHCl}_3} -\overset{|}{C}{-}N{-}R \quad (\text{ring closed by } CCl_2)$$

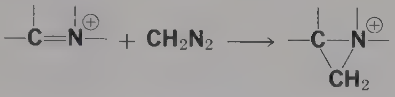
There are a few reports in the literature of the preparation of aziridines by the addition of a divalent species to a C=N bond, analogous to reactions **6-62** and **6-63.**[210] In the example shown above[211] the attacking species is probably dichlorocarbene. Iminium ions have been converted to quaternary aziridinium salts with diazomethane:[212]

---

[209] Schönberg and Frese, *Chem. Ber.* **95,** 2810 (1962).

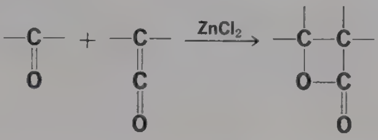
[210] For a review, see Kirmse, "Carbene Chemistry," pp. 179–182, Academic Press Inc., New York, 1964.

[211] Fields and Sandri, *Chem. Ind.* (*London*) **1959,** 1216.

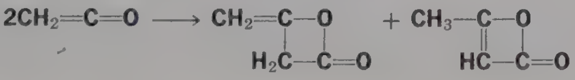


The reaction has also been performed with sulfur ylides.[207]

6-65 The formation of β-lactones from ketenes

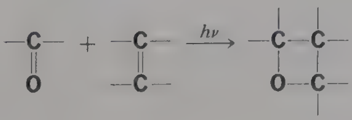


Aldehydes, ketones, and quinones react with ketenes to give β-lactones, with diphenylketene being used most often.[213] The reaction is catalyzed by Lewis acids, and without them most ketones do not give adducts, because the adducts decompose at the high temperatures necessary when no catalyst is used. Ketene adds to another molecule of itself:



This dimerization is so rapid that ketene does not form β-lactones with aldehydes or ketones, except at low temperatures. Other ketenes dimerize more slowly. In these cases the major dimerization product is not the β-lactone, but a cyclobutenone (see p. 636). However, the proportion of ketene which dimerizes to β-lactone may be increased by the addition of catalysts such as $ZnCl_2$ or triethylamine.[214]

Ordinary aldehydes and ketones can add to olefins to give oxetanes:



This reaction occurs under the influence of ultraviolet light. The yields are quite low, except for fluorinated olefins.

OS **III**, 508. For the reverse reaction, see OS **45**, 50.

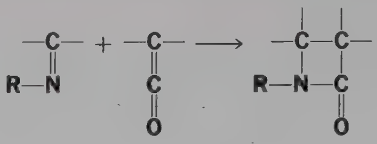
---

[212] Leonard, Jann, Paukstelis, and Steinhardt, *J. Org. Chem.* **28**, 1499 (1963).

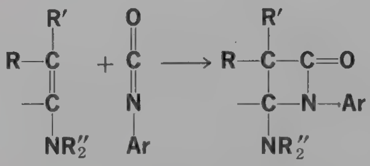
[213] For reviews, see Zaugg, *Org. Reactions* **8**, 305–363 (1954), pp. 313–315; Lacey, *Advan. Org. Chem.* **2**, 213–263 (1960), pp. 226–228.

[214] Farnum, Johnson, Hess, Marshall, and Webster, *J. Am. Chem. Soc.* **87**, 5191 (1965).

6-66 The formation of β-lactams from ketenes



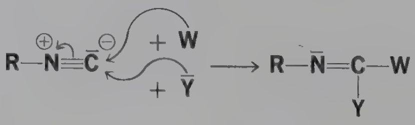
Ketenes add to imines to give β-lactams.[215] The reaction is generally carried out with ketenes of the form $R_2C{=}C{=}O$. It has not been successfully applied to $RCH{=}C{=}O$. It has been done with ketene, but the more usual course with this reagent is an addition to the enamine tautomer of the substrate. β-Lactams have also been prepared in the opposite manner: by the addition of enamines to isocyanates:[216]



The reaction applies only to enamines derived from ketones. Those derived from aldehydes react with isocyanates but do not give four-membered rings.

There are no *Organic Syntheses* references, but see OS **46,** 51, for a related reaction.

Addition to Isonitriles. Addition to $R{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{C}$ is not simply a matter of a species with an electron pair adding to one atom, and a species without a pair adding to the other, as is addition to the other types of double and triple bonds in this chapter and in Chapter 15. In these additions the electrophile and the nucleophile *both add to the carbon.* No species adds to the nitrogen, which however loses its positive charge by obtaining as an unshared pair one of the triple-bond pairs of electrons:



50

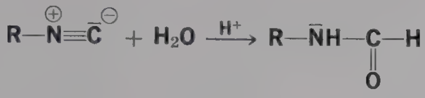
In each of the reactions considered below, **50** undergoes a further reaction, so that the product is of the form $R{-}\ddot{N}H{-}\overset{|}{\underset{|}{C}}{-}$.

---

[215] For a review, see Sheehan and Corey, *Org. Reactions* **9,** 388–408 (1957), pp. 395–399.

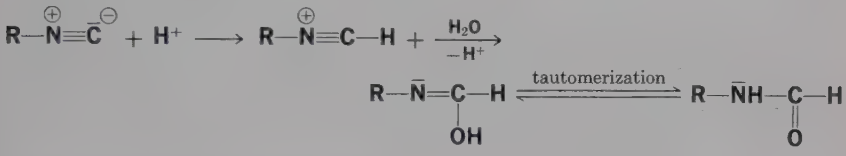
[216] Perelman and Mizsak, *J. Am. Chem. Soc.* **84,** 4988 (1962).

6-67 The addition of water to isonitriles



$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\bar{C}} + H_2O \xrightarrow{H^+} R-\bar{N}H-\underset{\underset{O}{\|}}{C}-H$$

Formamides may be prepared by the acid-catalyzed addition of water to isonitriles. The mechanism is probably as follows:[217]

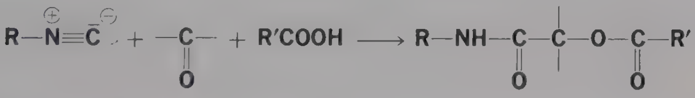


6-68 The reduction of isonitriles

$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\bar{C}} + LiAlH_4 \longrightarrow R-NH-CH_3$$

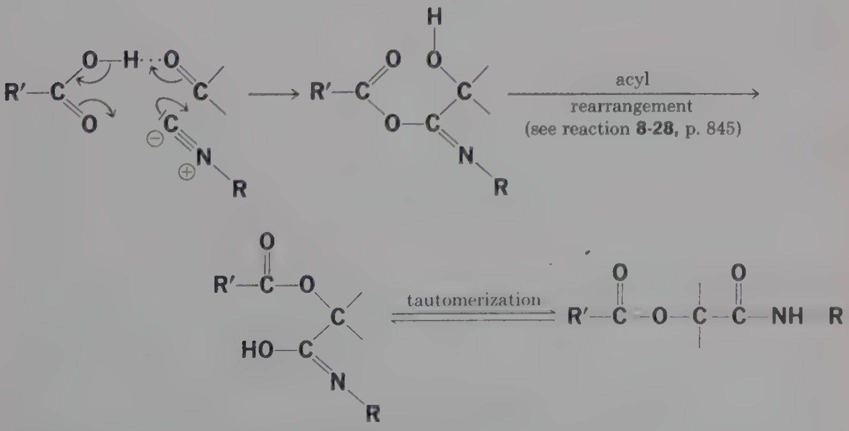
Isonitriles have been reduced to N-methylamines with lithium aluminum hydride.

6-69 The Passerini and related reactions[218]



$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\bar{C}} + -\underset{\underset{O}{\|}}{C}- + R'COOH \longrightarrow R-NH-\underset{\underset{O}{\|}}{C}-\overset{|}{\underset{|}{C}}-O-\underset{\underset{O}{\|}}{C}-R'$$

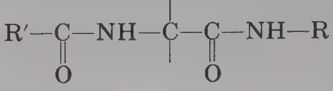
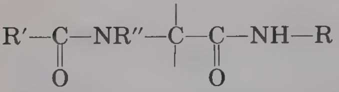
When an isonitrile is treated with a carboxylic acid and an aldehyde or ketone, an α-acyloxy amide is prepared. This is called the *Passerini reaction,* and the following mechanism has been postulated:

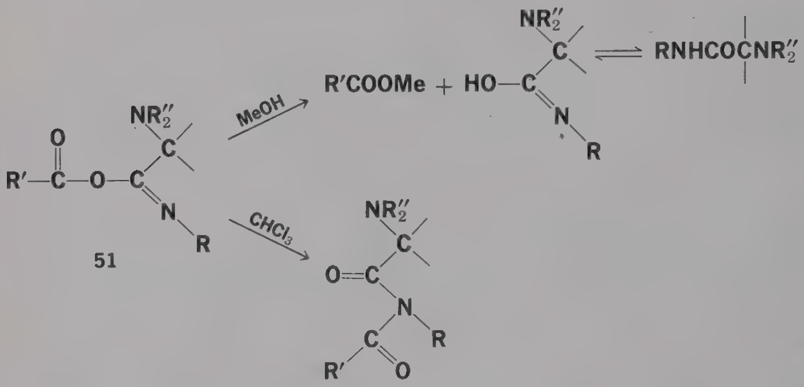


---

[217] Drenth, *Rec. trav. chim.* **81**, 319 (1962).

[218] For a review, see Ugi, *Angew. Chem. Intern. Ed. Engl.* **1**, 8–21 (1962).

If ammonia or a primary amine is also added to the mixture, the product is the corresponding bisamide  $R'-\underset{\underset{O}{\|}}{C}-NH-\overset{|}{\underset{|}{C}}-\underset{\underset{O}{\|}}{C}-NH-R$ (from NH_3) or  $R'-\underset{\underset{O}{\|}}{C}-NR''-\overset{|}{\underset{|}{C}}-\underset{\underset{O}{\|}}{C}-NH-R$ (from $R''NH_2$). This product probably arises from a reaction between the carboxylic acid, the isonitrile, and the *imine* formed from the aldehyde or ketone and ammonia or the primary amine. When a secondary amine ($R_2''NH$) is used, then the initial addition product (**51**) cannot undergo an acyl rearrangement of the same type. In methanol the acyl group cleaves, and the product is an α-amino amide, while in chloroform the acyl group migrates to the *other* nitrogen:

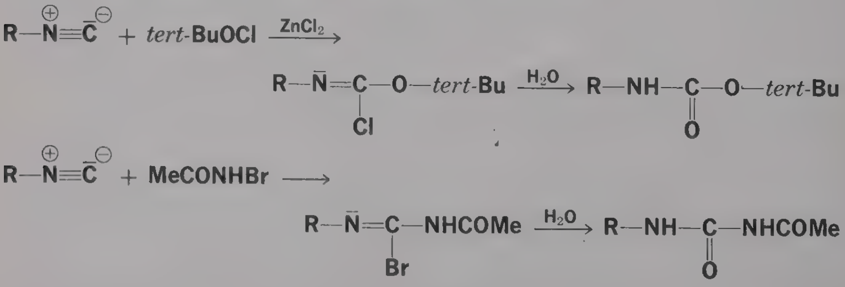


51

and the product is an imide containing a tertiary amine function.

Similar reactions may be carried out with an isonitrile, an aldehyde or ketone, and ammonia or an amine, but with some other YH substituting for the carboxylic acid (for example, H_2O, HN_3, HNCO, etc.).

6-70 The addition of O- and N-halides to isonitriles



$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\underline{C}} + tert\text{-}BuOCl \xrightarrow{ZnCl_2} R-\bar{N}=\underset{\underset{Cl}{|}}{C}-O-tert\text{-}Bu \xrightarrow{H_2O} R-NH-\underset{\underset{O}{\|}}{C}-O-tert\text{-}Bu$$

$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\underline{C}} + MeCONHBr \longrightarrow R-\bar{N}=\underset{\underset{Br}{|}}{C}-NHCOMe \xrightarrow{H_2O} R-NH-\underset{\underset{O}{\|}}{C}-NHCOMe$$

Alkyl hypochlorites and N-halo amides add to isonitriles to give, after hydrolysis, urethanes and N-acylureas (ureides), respectively.[219]

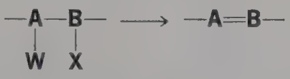
---

[219] Okano, Ito, Shono, and Oda, *Bull. Chem. Soc. Japan* **36**, 1314 (1963).

CHAPTER SEVENTEEN

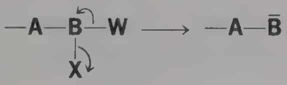
Eliminations

When two groups are lost from adjacent atoms so that a new double (or triple) bond is formed

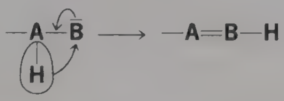


$$-\underset{\substack{|\\ W}}{A}-\underset{\substack{|\\ X}}{B}- \longrightarrow -A{=}B-$$

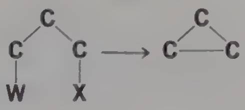
the reaction is called *β-elimination,* with one atom called the α and the other the β atom. In an α-elimination both groups are lost from the same atom, to give a carbene (or a nitrene):



This species may undergo a variety of reactions (see p. 164), but only when a hydrogen is present on A can a new double bond be formed, by a hydride shift:



In a γ-elimination, a three-membered ring is formed:

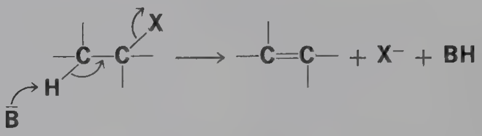


Some of these processes were discussed in Chapter 10. In this chapter only reactions leading to double or triple bonds are considered, which means that we are largely restricting ourselves to β-eliminations. β-Eliminations in which X and W are both hydrogen are oxidation reactions and are treated in Chapter 19.

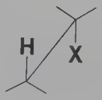
MECHANISMS AND ORIENTATION

β-Elimination reactions may be divided into two types, with one type taking place largely in solution, and the other (pyrolytic eliminations) mostly in the gas phase. In the reactions in solution one group leaves with its electrons, and the other without, the latter most often being hydrogen. In these cases we shall refer to the former group as the *leaving group*. This type of process may also occur in the pyrolytic reactions, but here there are also two other possibilities, a free-radical elimination and a cyclic mechanism (see p. 747). In most β-eliminations the new bonds are C=C or C≡C, and our discussion of mechanisms is largely confined to these cases.[1] Mechanisms in solution (E2, E1, E1cB) are discussed first.

The E2 Mechanism. In the E2 mechanism (elimination, bimolecular), the two groups depart simultaneously, with the proton being pulled off by a base:[2]



The mechanism thus takes place in one step and kinetically is second order: first order in substrate and first order in base. It is analogous to the S_N2 mechanism (p. 251) and often competes with it. With respect to the substrate, the difference between the two pathways is whether the species with the unshared pair attacks the carbon (and thus acts as a nucleophile) or the hydrogen (and thus acts as a base). In most cases it has been found that the E2 reaction, like the S_N2, is stereospecific: that the five atoms involved (including the base) must be in one plane, and that H and X must be trans.[3] This conformation of H and X



is called *anti-periplanar*. The dihedral angle between H and X is 180°. As in the case of the S_N2 mechanism, the leaving group may be positive or neutral, and the base may be negatively charged or neutral.

Some of the evidence for the existence of the E2 mechanism is as follows:

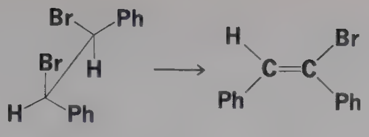
1. The reaction displays the proper second-order kinetics.
2. If the elimination of HBr from *meso*-1,2-dibromo-1,2-diphenylethane is indeed trans, then the resulting olefin should be *cis*-α-bromostilbene, while the D or L isomer should give the trans olefin:

---

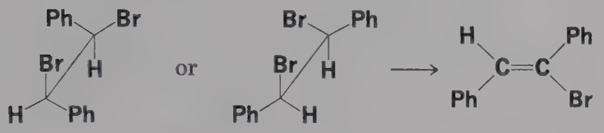
[1] For a monograph on elimination mechanisms, see Banthorpe, "Elimination Reactions," Elsevier Publishing Company, New York, 1963. For reviews, see, in Patai, "The Chemistry of Alkenes," Interscience Publishers, Inc., New York, 1964, the articles by Saunders, pp. 149–201 (eliminations in solution), and Maccoll, pp. 203–240 (pyrolytic eliminations). Also see Grigor'eva and Kucherov, *Russ. Chem. Rev.* **31,** 18–35 (1962); and Köbrich, *Angew. Chem. Intern. Ed. Engl.* **4,** 49–68 (1965), pp. 59–63 (for the formation of triple bonds).

[2] For a review, see Bunnett, *Angew. Chem. Intern. Ed. Engl.* **1,** 225–235 (1962).

[3] A theoretical explanation for this stereospecificity has been offered by Fukui and Fujimoto, *Tetrahedron Letters* **1965,** 4303.

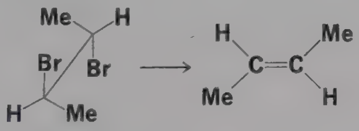


meso cis

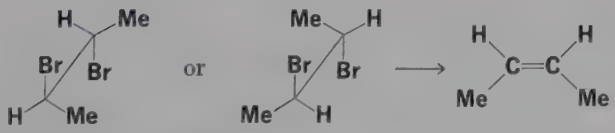


DL pair trans

This experiment was tried in 1904, and this is exactly what occurred.[4] Many similar examples have been found since then. Obviously, this type of experiment need not be restricted to compounds which have a meso form. Trans elimination requires that an erythro DL pair (or either isomer) give the cis olefin, and the threo DL pair (or either isomer) give the trans isomer, and this has been found many times. Trans elimination has also been demonstrated in cases where the positive leaving group is not hydrogen. In the reaction of 2,3-dibromobutane with iodide ion, the two bromines are removed (reaction **7-22**). In this case the meso compound gave the trans olefin and the DL pair the cis:[5]



meso trans



DL pair cis

3. In open-chain compounds the molecule can usually adopt that conformation in which H and X are anti-periplanar. However, in cyclic systems this is not always the case. There are nine stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane, seven meso forms and a DL pair (see p. 99). Four of the meso compounds and the DL pair (all that were then known) were subjected to elimination of HCl. Only one of these (**1**, called the β-isomer) has no Cl trans to an H. Of the other isomers, the fastest elimination rate was about three times as fast as the slowest, but the rate for **1** was 7000 times slower than that of the slowest of the other isomers.[6] This result demon-

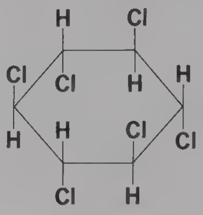
---

[4] Pfeiffer, *Z. physik. Chem.* **48**, 40 (1904).

[5] Winstein, Pressman, and Young, *J. Am. Chem. Soc.* **61**, 1645 (1939).

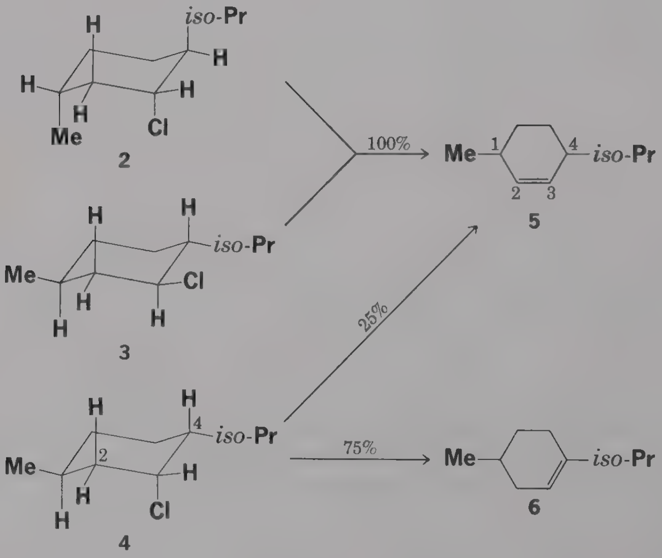
[6] Cristol, *J. Am. Chem. Soc.* **69**, 338 (1947); Cristol, Hause, and Meek, *J. Am. Chem. Soc.* **73**, 674 (1951).

strates that E2 elimination in cyclic systems proceeds best when the H and X are trans. However, there is an additional restriction. Adjacent trans groups on a six-membered ring may be diaxial or diequatorial (p. 106), and



1

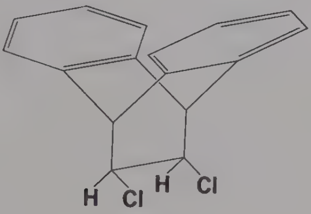
the molecule is generally free to adopt either conformation, though one may have a higher energy than the other. Anti-periplanarity of the leaving groups requires that they be diaxial, even if this is the conformation of higher energy. The results with menthyl and neomenthyl chlorides are easily interpretable on this basis. Menthyl chloride has two chair conformations, **2** and **3**. **3**, in which the three substituents are all equatorial, is the more stable. The more stable chair conformation of neomenthyl chloride is **4**, in which the chlorine is axial, and there are axial hydrogens on both C-2 and C-4. The results are: neomenthyl chloride gives rapid E2 elimination, and the olefin produced is predominantly **6** (**6**:**5** ratio is about **3**:**1**), in accord with Zaitsev's rule (p. 739). Since an axial hydrogen is available on both sides, this factor does not control the direction of elimination, and Zaitsev's rule is free to operate. However, for menthyl chloride, elimination is much slower, and the product is entirely the anti-Zaitsev **5**. It is slow because the



unfavorable conformation **2** had to be achieved before elimination could take place, and the product is **5** because only on this side is there an axial hydrogen.[7]

4. That trans elimination also occurs in the formation of triple bonds is shown by elimination from *cis*- and *trans*-HOOC—CH=CCl—COOH. In this case the product in both cases is HOOCC≡CCOOH, but the trans isomer reacts about fifty times as fast as the cis compound.[8]

5. In compound **7**, each Cl has an adjacent hydrogen trans to it, and if planarity of leaving groups were not required, elimination would be normal.



7

However, the crowding of the rest of the molecule forces the hydrogens and chlorines to be eclipsed, and planarity cannot be obtained. Elimination from **7** is much slower than from corresponding nonbridged compounds.[9]

6. When the leaving hydrogen is replaced by deuterium in second-order eliminations, there is an isotope effect of from 3 to 8, consistent with breaking of this bond in the rate-determining step.[10]

We have seen a number of examples in which trans elimination was much faster than cis elimination. Nevertheless, there still was elimination even where the leaving groups had to be cis. For example, **1** still underwent elimination, though much more slowly than the other isomers. For a number of years attempts have been made to explain this cis elimination, since it is incompatible with the E2 mechanism as shown on page 728. One of these explanations[11] is that a dihedral angle of 180° is not the only possible angle for an E2 elimination, but that elimination may also occur when the angle is 0°, that is, from a syn-periplanar conformation. Arguments from orbital-overlap considerations lead to the prediction that the transition state must be coplanar, but either 180 or 0° will fit this argument. It may be that the 0° angle is rare because it requires the leaving groups to be eclipsed, and that they adopt this pathway only when the other is impossible. A result in accord with cis elimination is the following: in **8, 9, 10,** and **11,** the direction of elimination is toward the phenyl group so that the new double bond may be stabilized by conjugation with the ring. Elimination from **8** was more than 10^4 times faster than from **9**, because, as we have seen, the leaving groups in **8** can adopt an anti-periplanar conformation while those in **9** cannot (the dihedral angle here is about 60°). However, in cyclopentanes, the substituents are almost eclipsed. As for the corresponding cyclohexanes, the cis isomer (**10**) reacted faster than the trans (**11**), but *the rate was only 14 times faster here.*[11] The normal dihedral angle in **10** is about 120°, but, by twisting, the molecule can bring this up to about 180°. Such an angle is impossible for **11**, but 0° is its *normal* angle. A cis E2 elimination was also shown in the case of **12**, which gave 94% of the product containing no deuterium.[12] Similar results were obtained with tosylates. In these cases the leaving groups prefer cis elimination, with a dihedral angle of 0°, to trans elimination, with a dihedral angle of about 120°. The rate is faster for the case where both groups can leave from the exo side of the molecule than it is where they must both leave from the endo side (as in the endo isomer of **12**).[13] Another fact in accord with this explanation is that the trans isomer of **7** (dihedral angle about 0°) actually reacted about *eight times faster* than **7**, where the angle is about 120°.[9] However, cis E2 elimination is not the only possible way of explaining these facts. Another explanation which has been suggested is that these eliminations proceed by the E1cB mechanism (p. 735), though there is Hammett ρ evidence that this is not happening in the case of **11**.[11] However, it is very difficult to distinguish between the possibility of a straight E2 mechanism with cis elimination and an E2 mechanism with considerable E1cB character (p. 737), also proceeding with cis elimination. Cis eliminations are very unlikely in open-chain systems, where free rotation can produce the anti-periplanar conformation, unless the rotation is blocked by very large groups.

---

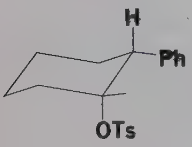
[7] Hughes, Ingold, and Rose, *J. Chem. Soc.* **1953,** 3839.

[8] Michael, *J. prakt. Chem.* **52,** 308 (1895).

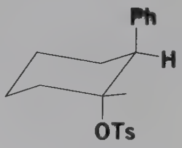
[9] Cristol and Hause, *J. Am. Chem. Soc.* **74,** 2193 (1952).

[10] See, for example, Saunders and Edison, *J. Am. Chem. Soc.* **82,** 138 (1960); Shiner and Smith, *J. Am. Chem. Soc.* **80,** 4095 (1958), **83,** 593 (1961).

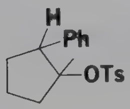
[11] DePuy, Thurn, and Morris, *J. Am. Chem. Soc.* **84,** 1314 (1962); DePuy, Morris, Smith, and Smat, *J. Am. Chem. Soc.* **87,** 2421 (1965).



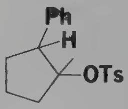
8



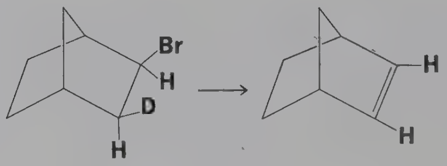
9



10



11

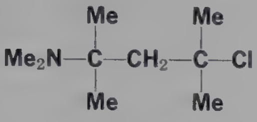


12

[12] Kwart, Takeshita, and Nyce, *J. Am. Chem. Soc.* **86**, 2606 (1964). See also Coke and Cooke, *J. Am. Chem. Soc.* **89**, 2779 (1967), for a similar result in the case of pyrolysis of a quaternary ammonium hydroxide.

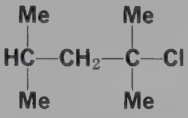
[13] LeBel, Beirne, and Subramanian, *J. Am. Chem. Soc.* **86**, 4144 (1964).

There is evidence that the E2 mechanism can be anchimerically assisted by a suitably situated neighboring group (see p. 263). Elimination of HCl (by solvolysis in 80% aqueous ethanol) proceeded 27 times faster from 4-dimethylamino-2,4-dimethyl-2-chloropentane (**13**) than from 2,4-dimethyl-2-chloropentane (**14**).[14] Furthermore, **13** gave only the 1-olefin, while **14** gave about 20% of the 2-isomer. The mechanism may be formulated:



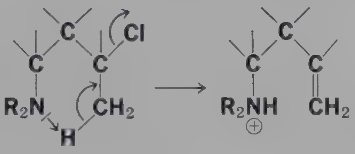
$\mathrm{Me_2N{-}\overset{Me}{\underset{Me}{C}}{-}CH_2{-}\overset{Me}{\underset{Me}{C}}{-}Cl}$

13

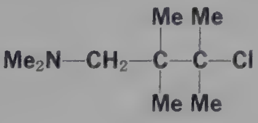


$\mathrm{H\overset{Me}{\underset{Me}{C}}{-}CH_2{-}\overset{Me}{\underset{Me}{C}}{-}Cl}$

14

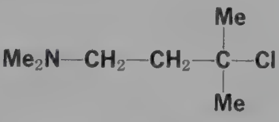


Other, similar, compounds also gave enhanced rates. For example, 4-dimethylamino-2,3,3-trimethyl-2-chlorobutane (**15**) reacted 125 times faster than the corresponding 2,3,3-trimethyl-2-chlorobutane. Apparently, either β or γ substitution is required, since 4-dimethylamino-2-methyl-2-chlorobutane (**16**) reacted *more slowly* than 2-methyl-2-chlorobutane.[14]



$\mathrm{Me_2N{-}CH_2{-}\overset{Me}{\underset{Me}{C}}{-}\overset{Me}{\underset{Me}{C}}{-}Cl}$

15



$\mathrm{Me_2N{-}CH_2{-}CH_2{-}\overset{Me}{\underset{Me}{C}}{-}Cl}$

16

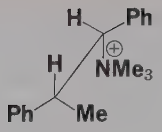
Eclipsing Effects in E2 Eliminations.[15] In the case of (1,2-diphenylpropyl)trimethylammonium ion, the threo DL pair (**17**) gave the trans olefin, and the erythro pair (**18**) gave the cis olefin, as expected for stereospecific trans elimination, but the threo pair reacted 57 times faster than the erythro (with $\mathrm{OEt^-}$ as the base).[16] For each isomer, the conformation necessary to achieve trans elimination is shown. In the threo isomer, the β phenyl group is completely staggered with respect to the other phenyl group, but in the erythro case the two phenyl groups are gauche. The latter is, of course, a higher-energy conformation than the former. Therefore, **17** may undergo elimination from its conformer of lowest energy, while **18** must adopt one of the higher-energy conformations, resulting in the lower rate. This type of effect is called an *eclipsing effect*. Note that eclipsing in the transition state, not in the ground state, is what matters.

---

[14] Braun, Ebner, Grob, and Jenny, *Tetrahedron Letters* **1965**, 4733.

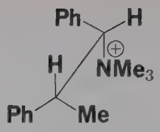
[15] For a discussion, see Cram, in Newman, "Steric Effects in Organic Chemistry," pp. 338–345, John Wiley & Sons, Inc., New York, 1956.

[16] Cram, Greene, and DePuy, *J. Am. Chem. Soc.* **78**, 790 (1956).



threo (one of the pair)

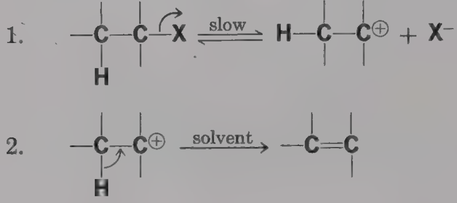
17



erythro (one of the pair)

18

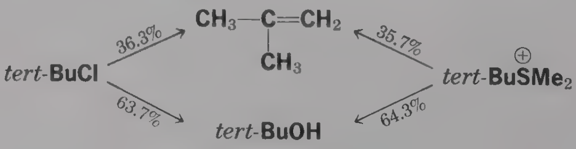
The E1 Mechanism. The E1 mechanism is a two-step process in which the rate-determining step is ionization of the substrate to give a carbonium ion which rapidly loses a β proton to a base, usually the solvent:



The E1 mechanism normally operates without an *added* base. Just as the E2 mechanism is analogous to and competes with the S_N2, so is the E1 mechanism related to the S_N1. In fact, the first step of the E1 is exactly the same as that of the S_N1 mechanism. The second step differs in that the solvent pulls a proton from the β carbon of the carbonium ion rather than attacking it at the positively charged carbon, as in the S_N1 process. In a pure E1 reaction (that is, without ion pairs, etc.) the product should be completely nonstereospecific, since the carbonium ion is free to adopt its most stable conformation before giving up the proton.

Some of the evidence for the E1 mechanism is as follows:

1. The reaction exhibits first-order kinetics (in substrate) as expected.
2. If the reaction is performed on two molecules which differ only in the leaving group (for example, *tert*-BuCl and *tert*-Bu$\overset{\oplus}{\mathrm{S}}\mathrm{Me}_2$) the rates should obviously be different since they depend on the ionizing ability of the molecule. However, once the carbonium ion is formed, if the solvent and the temperature are the same, it should suffer the same fate in both cases, since the nature of the leaving group does not affect the second step. This means that *the ratio of elimination to substitution should be the same.* The compounds mentioned in the example were solvolyzed at 65.3° in 80% aqueous ethanol, with the following results:[17]



---

[17] Cooper, Hughes, Ingold, and MacNulty, *J. Chem. Soc.* **1948**, 2038.

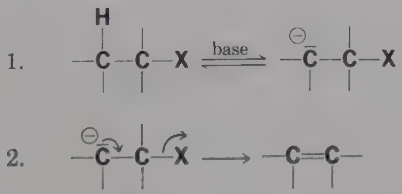
Although the rates were greatly different (as expected with such different leaving groups), the product ratios were the same, within 1%. If this had taken place by a second-order mechanism, the nucleophile would not be expected to have the same ratio of preference for attack at the β hydrogen compared to attack at a *neutral* chloride as for attack at the β hydrogen compared to attack at a *positive* SMe_2 group.

3. Many reactions carried out under first-order conditions proceed quite readily to give olefins where a cis hydrogen must be removed, often in preference to the removal of a trans hydrogen. For example, menthyl chloride (**2**, p. 730), which by the E2 mechanism gave only **5**, under E1 conditions gave 68% **6** and 32% **5**, since the steric nature of the hydrogen is no longer a factor here, and the more stable olefin (Zaitsev's rule, p. 739) is predominantly formed.

4. If carbonium ions are intermediates, we should expect rearrangements with suitable substrates. These have often been found in elimination reactions performed under E1 conditions.

It has been shown that E1 reactions can involve ion pairs, just as is true for S_N1 reactions (p. 259).[18] This effect is naturally greatest for nondissociating solvents: it is least in water, greater in ethanol, and greater still in acetic acid.

The E1cB Mechanism. In the E1 mechanism, X leaves first and then H. In the E2 mechanism the two groups leave at the same time. There is a third possibility: the H leaving first, and then the X. This is a two-step process, called the *E1cB mechanism*, or the *carbanion mechanism*, since the intermediate is a carbanion:



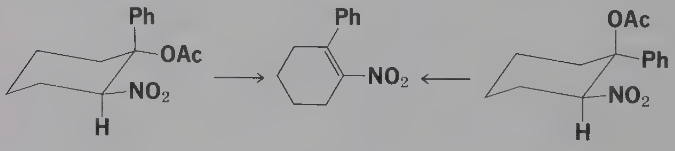
This is a second-order mechanism, because both the base and the substrate are present in the rate-determining step. The name E1cB comes from the fact that it is the conjugate base of the substrate which is giving up the leaving group (see the S_N1cB mechanism, p. 293). The existence of this mechanism is much less firmly established than that of the E1 or E2 mechanisms. Some of the experimental work used to support it has also been explained in other ways. For example, the fact that cis elimination is sometimes found in second-order reactions has been used to lend support to this mechanism, but this has also been explained as a simple E2 cis-elimination process (p. 731). The following is some of the other evidence in support of the E1cB mechanism:

---

[18] Cocivera and Winstein, *J. Am. Chem. Soc.* **85**, 1702 (1963).

1. The first step of the E1cB mechanism involves a reversible exchange of protons between the substrate and the base. In that case, if deuterium is present in the base, then recovered starting material should contain deuterium. This was found to be the case in the treatment of $Cl_2C{=}CHCl$ with NaOD to give $ClC{\equiv}CCl$. When the reaction was stopped before completion, there *was* deuterium in the recovered olefin.[19] A similar result was found for pentahaloethanes.[20] It would be expected that the E1cB mechanism would be most likely where there is some structural factor in the substrate which increases the acidity of the hydrogen. Since hydrogens on a double-bond carbon (sp^2) are more acidic than those on sp^3 carbons, it may be expected that the E1cB mechanism would be more likely to be found in eliminations yielding triple bonds than in those giving double bonds. Another likely place for the E1cB mechanism should be in reaction of a substrate like $PhCH_2CH_2Br$, since the carbanion would be stabilized by resonance with the phenyl group. Nevertheless, no deuterium exchange was found here.[21] If this type of evidence is a guide, then it may be inferred that the E1cB mechanism is quite rare. However, it must be pointed out that neither the positive nor the negative deuterium-exchange results constitute absolute proof of the existence or nonexistence of the E1cB mechanism. The mechanism may be occurring, and yet no exchange may be found, *if the carbanion goes to product much faster than it reverts to starting material.* On the other hand, it has been pointed out[22] that deuterium exchange could be taking place without the carbanion *necessarily* being the species which loses the leaving group.

2. In the elimination of acetic acid from 2-phenyl-2-acetoxy-1-nitrocyclohexane the isomer in which the H and OAc were cis (**19**) reacted four times faster than the one in which these groups were trans (**20**).[23] Evidence



19

20

against a cis E2 elimination in this case was that an increase in solvent polarity or ionic strength increased the rates of both reactions, arguing against a mechanism not involving ions, and that the Hammett ρ value was positive, and identical for the two substrates. This substrate is a favorable one for carbanion formation, because the acidity of the β hydrogen is increased by the presence of the nitro group.

---

[19] Houser, Bernstein, Miekka, and Angus, *J. Am. Chem. Soc.* **77**, 6201 (1955).

[20] Hine, Wiesboeck, and Ghirardelli, *J. Am. Chem. Soc.* **83**, 1219 (1961); Hine, Wiesboeck, and Ramsay, *J. Am. Chem. Soc.* **83**, 1222 (1961).

[21] Skell and Hauser, *J. Am. Chem. Soc.* **67**, 1661 (1945).

[22] Breslow, *Tetrahedron Letters* **1964**, 399.

[23] Bordwell and Garbisch, *J. Org. Chem.* **28**, 1765 (1963); Bordwell, Arnold, and Biranowski, *J. Org. Chem.* **28**, 2496 (1963).

3. For the case of ArCOCHClCHClAr, a rather complicated rate equation was followed, which is just the one predicted on the basis of the E1cB mechanism.[24]

4. In Michael-type additions to C=C bonds, a nucleophile attacks first, and then the hydrogen (p. 568). By the law of microscopic reversibility, those eliminations which are the reverse of Michael-type additions should start with the loss of a proton, and hence be E1cB processes. This has been shown to be the case.[25] It may be recalled that benzyne formation (p. 493) was also postulated to occur by such a process.

In many eliminations to form C=O and C≡N bonds the initial step is loss of a positive group (normally a proton) from the oxygen or nitrogen. These may also be regarded as E1cB processes.

The E1-E2-E1cB Spectrum. In the three mechanisms so far considered the similarities are greater than the differences. In each case there is a leaving group which comes off with its pair of electrons and another group (usually hydrogen) which comes off without them. The only difference is in the order of the steps. It is now generally accepted that there is a spectrum of mechanisms ranging from one extreme, in which the leaving group departs well before the proton (pure E1) to the other extreme, in which the proton comes off first, and then after some time, the leaving group follows (pure E1cB). The pure E2 case would be somewhere in the middle, with both groups leaving simultaneously. However, most reactions do not follow any of the three cases exactly, but fall somewhere in between, for example, the leaving group departing just before the proton. The latter case might be described as an E2 reaction with a small amount of E1 character. The concept may be expressed by the question: in the transition state, which bond (C—H or C—X) has undergone more cleavage?[26]

One way to determine just where a given reaction stands on the E1-E2-E1cB spectrum is to study isotope effects, which ought to tell something about the behavior of bonds in the transition state. For example, $CH_3CH_2\overset{\oplus}{N}Me_3$ showed a nitrogen isotope effect (k^{14}/k^{15}) of 1.017, while $PhCH_2CH_2\overset{\oplus}{N}Me_3$ gave a corresponding value of 1.009.[27] It would be expected that the phenyl group would move the reaction toward the E1cB side of the line, which means that for this compound the C—N bond is not so greatly broken in the transition state as it is for the unsubstituted one. The isotope effect bears this out, for it shows that, in the phenyl compound, the mass of the nitrogen has less effect on the reaction rate than it does in the unsubstituted compound. Similar results have been obtained with $\overset{\oplus}{S}R_2$ leaving groups, by the use of $^{32}S/^{34}S$ isotope effects.[28] The position of reactions along the spectrum has also been studied from the other side of the newly forming double bond, by the use of H/D and H/T isotope effects.[29]

---

[24] Crowell, Wall, Kemp, and Lutz, *J. Am. Chem. Soc.* **85**, 2521 (1963).

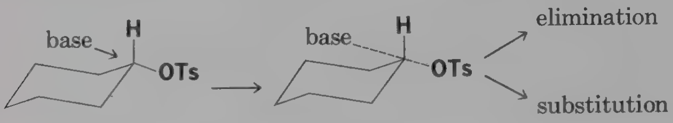
[25] Patai, Weinstein, and Rappoport, *J. Chem. Soc.* **1962**, 1741.

[26] This concept has been summarized by Bunnett, Ref. 2.

[27] Ayrey, Bourns, and Vyas, *Can. J. Chem.* **41**, 1759 (1963). Also see Simon and Müllhofer, *Chem. Ber.* **96**, 3167 (1963), **97**, 2202 (1964), *Pure Appl. Chem.* **8**, 379, 536 (1964).

[28] Saunders and Zimmerman, *J. Am. Chem. Soc.* **86**, 3789 (1964); Saunders, Cockerill, Ašperger, Klasinc, and Stefanović, *J. Am. Chem. Soc.* **88**, 848 (1966).

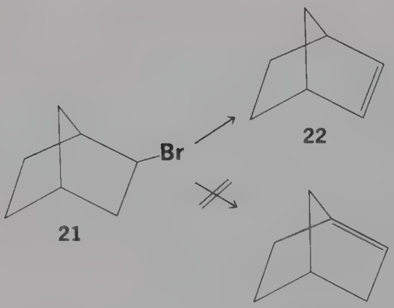
The Merged Substitution-Elimination Mechanism. The following mechanism was proposed for elimination from cyclic tosylates:[30]



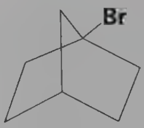
In this mechanism, called the *merged substitution-elimination mechanism,* there is no E2 transition state but only an S_N2 transition state, which, however, gives not only substitution but also elimination. The mechanism was proposed to account for the facts that (1) the reaction was second order and hence not E1; and (2) an axial OTs and an equatorial OTs *both* gave substantial amounts of elimination product, even though by the E2 mechanism, the axial group should give more. Though there is some evidence for this mechanism, it is not fully accepted.[31]

Orientation of the Double Bond. With some substrates, a β hydrogen is present on only one carbon, and (barring rearrangements) there is no doubt as to the identity of the product. For example, $PhCH_2CH_2Br$ can give only $PhCH{=}CH_2$. However, in many other cases two or three olefinic products are possible. In the simplest such case, a *sec*-butyl compound may give either 1-butene or 2-butene. There are a number of rules which enable us to predict, in many instances, which product will predominantly form.

1. No matter what the mechanism, a double bond does not go to a bridgehead carbon, unless the ring sizes are large. This means, for example, not only that **21** gives only **22** and not **23** (indeed **23** is not a known compound),



21 **22** **23**



24

---

[29] For example, see Saunders and Edison, *J. Am. Chem. Soc.* **82**, 138 (1960); Hodnett and Sparapany, *Pure Appl. Chem.* **8**, 385, 537 (1964); and Simon and Müllhofer, Ref. 27.

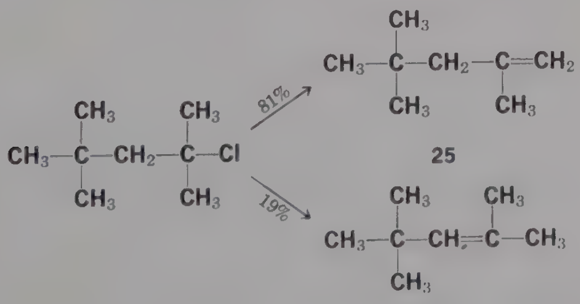
[30] Winstein, Darwish, and Holness, *J. Am. Chem. Soc.* **78**, 2915 (1956).

[31] For discussions, see Saunders, Ref. 1, pp. 162–164; Banthorpe, Ref. 1, pp. 37–40.

but also that **24** does not undergo elimination. This is known as *Bredt's rule.*

2. No matter what the mechanism, if there is a double bond (C=C or C=O) already in the molecule which can be in conjugation with the new double bond, then the conjugated product usually predominates, sometimes even when the stereochemistry is unfavorable.

3. In the E1 mechanism the leaving group is gone before the choice is made as to which direction the new double bond takes. Therefore the direction is determined almost entirely by the relative stabilities of the two (or three) possible olefins. In such cases *Zaitsev's rule*[32] operates. This rule states that *the double bond goes toward the most highly substituted carbon.* That is, a *sec*-butyl compound will give more 2-butene than 1-butene, and 3-bromo-2,3-dimethylpentane will give more 2,3-dimethyl-2-pentene than either 3,4-dimethyl-2-pentene or 2-ethyl-3-methyl-1-butene. Thus Zaitsev's rule predicts that the olefin predominantly formed will be the one with the largest possible number of alkyl groups on the C=C carbons, and in most cases this is what is found. From heat-of-combustion data (see p. 25) it is known that olefin stability increases with alkyl substitution, though just why this should be is a matter of conjecture. The most common explanation is hyperconjugation. For E1 eliminations Zaitsev's rule governs the orientation, whether the leaving group is neutral or positive, since, as already mentioned, the leaving group is not present when the choice of direction is made. This statement does not hold for E2 eliminations, and it may be mentioned here, for contrast with later results, that E1 elimination of $Me_2CHCHMe\overset{\oplus}{S}Me_2$ gave 91% of the Zaitsev product and 9% of the other.[33] However, there *are* cases in which the leaving group affects the direction of the double bond in E1 eliminations.[34] This may be attributed to ion pairs: that is, the leaving group is not completely gone when the hydrogen departs. Zaitsev's rule breaks down in cases where the non-Zaitsev product is more stable for steric reasons. Thus, E1 elimination of 2,4,4-trimethyl-2-chloropentane gives[35]



25

26

---

[32] Often given the German spelling: Saytzeff.

[33] de la Mare, *Progr. Stereochem.* **1**, 112 (1954).

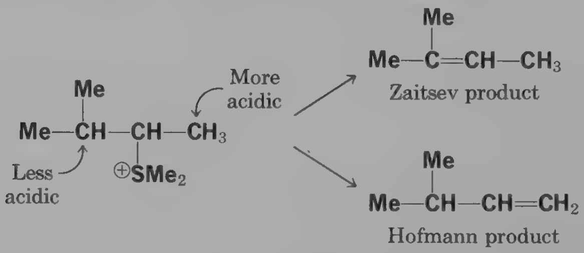
[34] Cram and Sahyun, *J. Am. Chem. Soc.* **85**, 1257 (1963); Silver, *J. Am. Chem. Soc.* **83**, 3482 (1961).

[35] Brown and Moritani, *J. Am. Chem. Soc.* **77**, 3607 (1955).

26 is less stable than **25** because it has a methyl group cis to a *tert*-butyl group.

4. In the E1cB mechanism, the data are scanty but seem to indicate that preference goes to the side with the more acidic β hydrogen.

5. For the E2 mechanism a trans proton is normally necessary, and if this is available in only one direction, that is the way the double bond will form. Because of the free rotation in acyclic systems (except where steric hindrance is great), this is a factor only in cyclic systems. Where trans β hydrogens are available on more than one carbon, the direction of double-bond formation in E2 reactions is mostly dependent on the nature of the leaving group. Since the base removes the proton in the rate-determining step, it would seem that relative acidity of the hydrogen should control the direction, as in E1cB reactions. However, this is true only where the leaving group is positively charged (and hence comes off as a neutral species), for example, $\overset{\oplus}{N}R_3$, $\overset{\oplus}{S}R_2$. These compounds obey Hofmann's rule: *the double bond goes in the direction which will give the least highly substituted olefin.* This is in accord with relative acidity, since electron-donating alkyl groups reduce the acidity at carbons to which they are connected. Thus, $Me_2CHCHMe\overset{\oplus}{S}Me_2$ gives more of the Hofmann product, under E2 conditions:



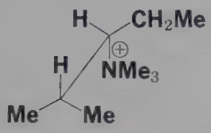
However, when the leaving group is neutral (and comes off as a negative ion), the orientation is reversed, and the Zaitsev product predominates, just as it does for the same substrates under E1 conditions, though of course the relative acidity of the protons remains the same. It seems that, for these compounds, olefin stability is what is important, and not acidity.[36]

Three explanations have been offered for this change in orientation with leaving group. The explanation of Hughes and Ingold is that acidity matters with charged and not with neutral leaving groups, because the charged groups exert a strong electron-withdrawing effect, making differences in acidity more manifest than they are with the less-electron-withdrawing neutral groups.[37] The explanation of Bunnett[2] is similar. According to this, the change to a positive leaving group causes the mechanism to shift toward the E1cB side of the spectrum, where there is more C—H bond breaking in the rate-determining step and where, consequently, acidity is more important. In this view, when there is a neutral leaving group, the mechanism will be more E1-like, C—X bond breaking will be more important, and olefin stability determines the direction of the new double bond. On the other hand, the third explanation, by H. C. Brown, is completely different. In this picture, inductive effects are unimportant, and the difference in orientation is largely a steric effect, caused by the fact that charged groups are usually larger than neutral ones. A CH_3 group is more open to attack than a CH_2R group, and a CHR_2 group is still less easily attacked. In addition, eclipsing effects are more important with increased substitution. For example, if we consider the case of $Me_2CHCH(\overset{\oplus}{N}Me_3)CH_2Me$, there is only one conformation (**27**) leading to Zaitsev elimination in which a hydrogen is trans to the leaving group, and this conformation is not the most stable one, since there is a methyl group and not a hydrogen between the two bulky groups CH_2Me and $\overset{\oplus}{N}Me_3$. On the other hand, for Hofmann elimination there are two conformations with trans hydrogens (**28** and **29**), and one of these (**28**) is the most stable, since the $CHMe_2$ group is between two hydrogens. In molecules with a CH_3 group, the situation is still more favorable, since elimination could occur from any conformation, and none of them can be gauche. Of course, these steric considerations also apply when the leaving group is neutral, but, according to Brown, they are much less important here because the neutral groups are smaller, do not block access to the hydrogens so much, and make the energy difference between the favorable and unfavorable conformations much less. Brown was able to show that Hofmann elimination increases with the size of the leaving group. Thus the percentage of 1-ene obtained from $CH_3CH_2CH_2CHXCH_3$ was as follows (X listed in order of increasing size): Br, 31%; I, 30%; OTs, 48%; $\overset{\oplus}{S}Me_2$, 87%; SO_2Me, 89%; $\overset{\oplus}{N}Me_3$, 98%.[38] Hofmann elimination was also shown to increase with increase in bulk of the substrate and of the attacking base.[39,40] With large enough compounds, Hofmann orientation may be obtained even with halides, e.g., *tert*-amyl bromide gave 89% of the Hofmann product. Even those who believe in the acidity explanations concede that these steric factors are operating in extreme cases.[41]

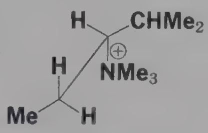
---

[36] Exceptions are known for both types of substrate. For example, see Gent and McKenna, *J. Chem. Soc.* **1959**, 137.

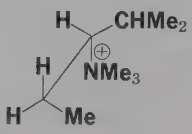
[37] For summaries of this position, see Ingold, *Proc. Chem. Soc.* **1962**, 265–274; Banthorpe, Hughes, and Ingold, *J. Chem. Soc.* **1960**, 4054; and Banthorpe, Ref. 1, pp. 55–59.



27



28



29

[38] Brown and Wheeler, *J. Am. Chem. Soc.* **78,** 2199 (1956).

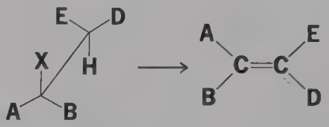
[39] Brown, Moritani, and Nakagawa, *J. Am. Chem. Soc.* **78,** 2190 (1956); Brown, Moritani, and Okamoto, *J. Am. Chem. Soc.* **78,** 2193 (1956); Brown and Nakagawa, *J. Am. Chem. Soc.* **78,** 2197 (1956); Brown and Moritani, *J. Am. Chem. Soc.* **78,** 2203 (1956).

[40] It has been maintained that the increase in Hofmann elimination which was attributed to an increase in the size of the attacking base was caused not by this factor, but by an increase in base strength and a solvent effect complementing each other: Froemsdorf, McCain, and Wilkison, *J. Am. Chem. Soc.* **87,** 3984 (1965); Froemsdorf, Dowd, and Leimer, *J. Am. Chem. Soc.* **88,** 2345 (1966).

[41] For example, see Banthorpe, Hughes, and Ingold, *J. Chem. Soc.* **1960,** 4054.

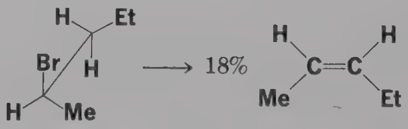
There is one result which seems to argue against the steric explanation: E2 elimination from $CH_3CH_2CH_2CHXCH_3$ when X was halogen gave the following percentages of 1-ene: F, 83%; Cl, 37%; Br, 25%; I, 20%.[42] However, there is some doubt as to whether this result is meaningful, since it is not certain that the steric requirements of the halogens *are* in the order $I > Br > Cl$.[43]

Steric Orientation of the Double Bond. When elimination takes place on a compound of the form CH_3—CABX or CHAB—CDDX, the new olefin does not have cis-trans isomerism, but for compounds of the form CHDE—CABX (D and E *not* H) (**30**) and CH_2D—CABX (**31**), cis and trans isomers are possible. When the mechanism is E2, **30** will give the isomer arising from trans orientation of X and H:

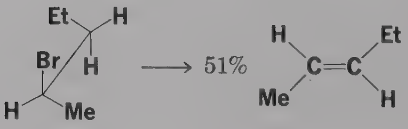


30

and as we have seen before (p. 729), an erythro compound gives the cis olefin and a threo compound the trans. For **31** there are two conformations possible for the transition state; these lead to different isomers, and often both are obtained. However, the one which predominates is determined by the eclipsing effect (p. 733). For example, Zaitsev elimination from 2-bromopentane can occur as follows:



32



33

However, in **32**, the ethyl group is between Br and Me, while, in **33**, it is between Br and H. This means that **33** is more stable, and most of the elimination should occur from this conformation. This is indeed what happens, and 51% of the trans isomer is formed (with KOEt) compared to

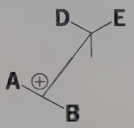
---

[42] Saunders, Fahrenholtz, Caress, Lowe, and Schreiber, *J. Am. Chem. Soc.* **87**, 3401 (1965). Similar results were obtained by Brown and Klimisch, *J. Am. Chem. Soc.* **88**, 1425 (1966).

[43] Saunders, Ref. 1, p. 193; Brown and Klimisch, Ref. 42.

18% of the cis (the rest is the Hofmann product).[44] These effects become larger with increasing size of A, B, and D.

For E1 eliminations, if there is a free carbonium ion:



(D may be H)

then it is free to rotate, and no matter what the geometry of the original compound, the more stable situation is the one where the larger of the D-E pair is opposite the smaller of the A-B pair, and the corresponding olefin should form. If the carbonium ion is not completely free, then to that extent, E2-type products are formed. Also, if a suitable neighboring group is present, there may be a neighboring-group effect, and this may affect the proportions of cis and trans olefins.

REACTIVITY

In this section we shall examine the effects of changes in the substrate, base, leaving group, and medium on (1) overall reactivity, (2) E1 versus E2 versus E1cB, and (3) elimination versus substitution.

Effect of Substrate Structure

1. *Effect on overall activity.* We shall refer to the carbon containing the leaving group (X) as the α-carbon, and to the carbon which loses the proton (or other positive species) as the β-carbon. Groups attached to the α- or β-carbons may exert at least four kinds of influence:

(*a*) They may stabilize or destabilize the incipient double bond (α or β groups may do this).

(*b*) They may stabilize or destabilize an incipient carbanion, affecting the acidity of the proton (β groups only).

(*c*) They may stabilize or destabilize an incipient carbonium ion (α groups only).

(*d*) They may exert steric effects (e.g., eclipsing effects) (both α and β groups).

Effects *a* and *d* may apply in all three mechanisms, though steric effects are greatest for the E2 mechanism. Effect *b* does not apply in the E1 mechanism, and effect *c* does not apply in the E1cB mechanism. Groups such as Ar and C=C increase the rates by any mechanism, whether they are α or β (effect *a*). Electron-withdrawing groups increase the acidity when in the β position, but have little effect in the α position, unless they also conjugate with the double bond. Thus Br, Cl, CN, Ts, NO_2, CN, SR in the β position all increase the rate of E2 eliminations.

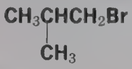
2. *Effect on E1 versus E2 versus E1cB.* α alkyl and α aryl groups increase

---

[44] Brown and Wheeler, *J. Am. Chem. Soc.* **78**, 2199 (1956).

TABLE 1. The effect of α and β branching on the rate of E2 elimination and on the amount of olefin formed

The reactions were between the alkyl bromide and OEt^-. The rate for isopropyl bromide was actually greater than that for ethyl bromide, if the temperature difference is considered. Neopentyl bromide, the next compound in the β-branching series, cannot be compared because it has no β hydrogen and cannot give an elimination product without rearrangement

Substrate	*Temperature*	*Olefin, %*	*Rate × 10^5 of E2 reaction*	*Reference*
CH_3CH_2Br	55°	0.9	1.6	45
$(CH_3)_2CHBr$	25°	80.3	0.237	46
$(CH_3)_3CBr$	25°	97	4.17	47
$CH_3CH_2CH_2Br$	55°	8.9	5.3	45
 $CH_3\underset{\displaystyle CH_3}{\underset{\vert}{C}H}CH_2Br$	55°	59.5	8.5	45

the extent of E1 elimination, since they stabilize the carbonium character of the transition state. That is, they shift the spectrum toward the E1 side. β alkyl groups also shift the mechanism toward E1, since they *decrease* the acidity of the hydrogen. However, β aryl groups shift the mechanism the other way (toward E1cB), since they stabilize the carbanion. This also applies to other β electron-withdrawing groups.

3. *Effect on elimination versus substitution.* Under second-order conditions α branching increases elimination, to the point where tertiary substrates undergo few S_N2 reactions, as we saw in Chapter 10. For example, Table 1 shows results on some simple akyl bromides.[45-47] Similar results were obtained with $\overset{\oplus}{S}Me_2$ as the leaving group.[48] Two reasons may be presented for this trend. One is statistical: as α branching increases, there are usually more hydrogens for the base to attack. The other is that α branching presents steric hindrance to attack of the base at the carbon. Under first-order conditions, increased α branching also increases the amount of elimination (E1 versus S_N1), though not so much, and usually the substitution product predominates. For example, solvolysis of *tert*-butyl bromide gave only 19% elimination[47] (compare with Table 1). β branching also increases the amount of E2 elimination with respect to S_N2 substitution (Table 1), not because elimination is faster but because the S_N2 mechanism is so greatly slowed (p. 281). Under first-order conditions too, β branching favors elimination over substitution, probably for steric reasons.[49] However, E2

---

[45] Dhar, Hughes, Ingold, and Masterman, *J. Chem. Soc.* **1948,** 2055.

[46] Dhar, Hughes, and Ingold, *J. Chem. Soc.* **1948,** 2058.

[47] Hughes, Ingold, and Maw, *J. Chem. Soc.* **1948,** 2065.

[48] Hughes, Ingold, and Maw, *J. Chem. Soc.* **1948,** 2072; Hughes, Ingold, Maw, and Woolf, *J. Chem. Soc.* **1948,** 2077; Hughes, Ingold, and Woolf, *J. Chem. Soc.* **1948,** 2084.

[49] Brown and Berneis, *J. Am. Chem. Soc.* **75,** 10 (1953).

eliminations from compounds with charged leaving groups are slowed by β branching. This is related to Hofmann's rule (p. 740).

4. Of course, compounds with the potential leaving group at a bridgehead do not give elimination reactions without rearrangement (p. 738).

Effect of the Attacking Base

1. *Effect on E1 versus E2 versus E1cB.* In the E1 mechanism, an external base is generally not required: the solvent acts as the base. Hence, when external bases are added, the mechanism is shifted toward E2. Stronger bases and higher base concentrations cause the mechanism to move toward the right of the E1-E2-E1cB spectrum (as we have written it). E2 elimination has been accomplished with the following bases:[50] H_2O, NR_3, OH^-, OAc^-, OR^-, OAr^-, NH_2^-, $CO_3^=$, $LiAlH_4$, I^-, CN^-, and organic bases. However, the only bases of preparative importance are OH^-, OR^-, and NH_2^-, usually in the conjugate acid as solvent.

2. *Effect on elimination versus substitution.* Strong bases not only benefit E2 as against E1, but also benefit elimination as against substitution. With a high concentration of strong base in a nonionizing solvent, bimolecular mechanisms are favored, and E2 predominates over S_N2. At low base concentrations, or in the absence of base altogether, in ionizing solvents, unimolecular mechanisms are favored, and the S_N1 mechanism predominates over the E1. In Chapter 10, it was pointed out that some species are strong nucleophiles, though weak bases (p. 288). The use of these obviously favors substitution. Some anions which do not promote elimination in protic solvents, where they are surrounded by a solvent shell, do so in aprotic solvents, where their affinity for protons is not satisfied by the solvent. For example, chloride ions normally give substitution and not elimination, but LiCl in acetone or dimethylformamide dehydrohalogenates many compounds. Even OH^- and OR^- are much more effective in the absence of protic solvents.[51]

Effect of the Leaving Group

1. *Effect on reactivity.* The leaving groups in elimination reactions are similar to those in nucleophilic substitution. E2 eliminations have been performed with the following groups: NR_3^+, PR_3^+, SR_2^+, OHR^+, SO_2R, OSO_2R, OCOR, OOH, OOR, F, Cl, Br, I, and CN (*not* OH_2^+). E1 eliminations have been carried out with: NR_3^+, SR_2^+, OH_2^+, OHR^+, OSO_2R, OCOR, Cl, Br, I, and N_2^+.[52] However, the only important leaving groups for preparative purposes are OH_2^+ (always by E1) and Cl, Br, I, and NR_3^+ (usually by E2).

2. *Effect on E1 versus E2 versus E1cB.* Better leaving groups shift the mechanism toward the E1 end of the spectrum, since they make ionization

---

[50] This list is from Banthorpe, Ref. 1, p. 4.

[51] For a discussion, see Banthorpe, Ref. 1, pp. 34–37.

[52] These lists are from Banthorpe, Ref. 1, pp. 4, 7.

easier. This effect has been studied in various ways. One way is by the measurement of Hammett ρ values for a series of substituted $ArCH_2CH_2X$, since these are a measure of the amount of carbanionic character on the β-carbon in the transition state. The greater the positive ρ value, the more carbanionic character in the transition state, and the farther is the reaction toward the E1cB end and away from the E1 end of the spectrum. A series of experiments of this kind gave the following ρ values for various leaving groups: F, 3.12; SMe_2^+, 2.75; Cl, 2.61; Br, 2.14; I, 2.07;[53] showing that indeed ρ does decrease with better leaving-group ability. However, even when F is the leaving group, isotope-effect studies have shown that a reversibly formed carbanion intermediate is absent.[54] Positively charged leaving groups shift the mechanism toward the E1cB end of the spectrum.

3. *Effect on elimination versus substitution.* As we have already seen (p. 734), for first-order reactions the leaving group has nothing to do with the competition between elimination and substitution, since it is gone before the decision is made as to which path to take. However, where ion pairs are involved, this is not true, and results have been found where the nature of the leaving group does affect the product.[55] In second-order reactions, the elimination/substitution ratio is not greatly dependent on a halide leaving group, though there is a slight increase in elimination in the order I > Br > Cl. When OTs is the leaving group, there is usually much more substitution. For example, n-$C_{18}H_{37}Br$ treated with *tert*-BuOK gave 85% elimination, while n-$C_{18}H_{37}OTs$ gave, under the same conditions, 99% substitution.[56] On the other hand, positively charged leaving groups increase the amount of elimination.

Effect of the Medium

1. *Effect of solvent on E1 versus E2 versus E1cB.* With any reaction a more polar environment enhances the rate of mechanisms which involve ionic intermediates. For neutral leaving groups, it may be expected that E1 and E1cB mechanisms will be aided by increasing polarity of solvent and by increasing ionic strength. There is evidence that the use of dimethyl sulfoxide as solvent moves the mechanism toward the E1cB side.[57] This solvent also promotes orientation according to Hofmann's rule rather than Zaitsev's.

2. *Effect of solvent on elimination versus substitution.* Increasing polarity of solvent favors S_N2 reactions at the expense of E2. In the classical example, alcoholic KOH is used to effect elimination, while the more polar aqueous KOH is used for substitution. Charge-dispersal discussions, similar to those on page 295,[58] only partially explain this. In most solvents S_N1 reactions

---

[53] DePuy and Froemsdorf, *J. Am. Chem. Soc.* **79**, 3710 (1957); DePuy and Bishop, *J. Am. Chem. Soc.* **82**, 2535 (1960).

[54] Saunders and Schreiber, *Chem. Commun.* **1966**, 145.

[55] For example, see Skell and Hall, *J. Am. Chem. Soc.* **85**, 2851 (1963), and Ref. 18.

[56] Veeravagu, Arnold, and Eigenmann, *J. Am. Chem. Soc.* **86**, 3072 (1964).

[57] Froemsdorf and McCain, *J. Am. Chem. Soc.* **87**, 3983 (1965); Froemsdorf, McCain, and Wilkison, *J. Am. Chem. Soc.* **87**, 3984 (1965).

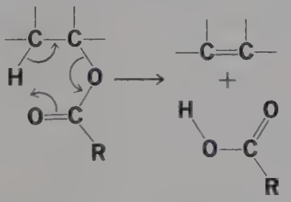
[58] Cooper, Dhar, Hughes, Ingold, MacNulty, and Woolf, *J. Chem. Soc.* **1948**, 2043.

are favored over E1. E1 reactions compete best in polar solvents which are poor nucleophiles.

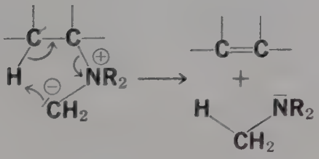
3. *Effect of temperature.* Elimination is favored over substitution by increasing temperature, whether the mechanism is first order or second order.[59]

MECHANISMS AND ORIENTATION IN PYROLYTIC ELIMINATIONS

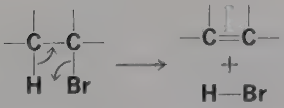
Mechanisms.[60] A number of types of compound undergo elimination on heating, with no other reagent present. Reactions of this type are often run in the gas phase. The mechanisms are obviously different from those already discussed, since all of those require a base (which may be the solvent) in one of the steps, and there is no base or solvent present in pyrolytic elimination. Three mechanisms have been found to operate. One of these involves a cyclic transition state, which may be either four-, five-, or six-membered. Examples of each size are:



(reaction **7-3**)

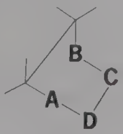


(reaction **7-7**)



(reaction **7-14**)

In this mechanism, which is called the *Ei mechanism,* the two groups leave at the same time and bond to each other as they are doing so. The elimination must be cis, and for the four- and five-membered transition states, the four or five atoms making up the ring must be coplanar. Coplanarity is not required for the six-membered transition state, since there is room for the outside atoms when the leaving atoms are staggered:

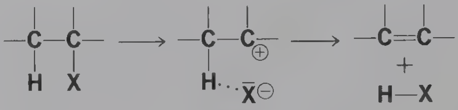


---

[59] Cooper, Hughes, Ingold, Maw, and MacNulty, *J. Chem. Soc.* **1948,** 2049.

[60] For reviews, see DePuy and King, *Chem. Rev.* **60,** 431 (1960); and Maccoll, Ref. 1; *Advan. Phys. Org. Chem.* **3,** 91–122 (1965).

Another mechanism is closely related to the Ei, but in this one the negative group leaves first, leaving behind a carbonium ion, which, in the second step, loses its β proton to the negative ion which has just come off. This is very like the E1 mechanism, except that, under these conditions, where there is nothing available to solvate the negative ion, it remains near the carbonium ion, so that an ion pair is the intermediate species:



We may call this the *ion-pair mechanism.* Some workers prefer to think of the intermediate as very polar, but not quite an ion-pair.[61] It is obvious that the ion-pair and the Ei mechanisms differ only in the timing of the steps involved, since in both of them it is the leaving group which takes the hydrogen. We may therefore envision a spectrum of mechanisms here, analogous to the E1-E2-E1cB spectrum: at one end the ion-pair mechanism, in which X breaks off first, as a negative ion; at the other end a mechanism in which H breaks off first as a proton; and in the middle a "pure" Ei mechanism with simultaneous cleavage. Here too we may speak of "an Ei mechanism with some ion-pair character," etc. Evidence for this picture is that the kinetics are first order, so that only one molecule of the substrate is involved in the reaction (that is, if one molecule were attacking another, the kinetics would be second order in substrate)[62] and that free-radical inhibitors do not slow the reactions, so that no free-radical mechanism is involved.[63] Evidence for the existence of the Ei mechanism is:

1. The mechanism predicts exclusive cis elimination, and this behavior has been found in many cases. The evidence is inverse to that for the E2 mechanism and generally involves the following facts: (1) an erythro isomer gives a trans olefin, and a threo gives a cis olefin; (2) the reaction takes place only when a cis β hydrogen is available; and (3) if, in a cyclic compound, a cis hydrogen is available on only one side, the elimination goes in that direction. We give here two examples of experimental evidence, neither of which exactly fits categories (1), (2), or (3). Elimination from the erythro (**34**) and threo (**35**) isomers of 1-acetoxy-2-deutero-1,2-diphenylethane gave in each case *trans*-stilbene, but the product from the erythro isomer retained 95% of the original deuterium, while the olefin obtained from the threo isomer retained only 26% of the deuterium.[64] In this case either the hydrogen or the deuterium could be cis to the acetoxy in either isomer, but the most favored conformations (shown) have the phenyls on opposite sides, and in these conformations **34** has a hydrogen nearest the acetoxy, and **35** a deuterium. This is an eclipsing effect. The reason that 95% is not balanced

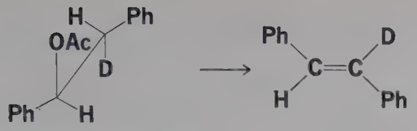
---

[61] Benson and Bose, *J. Chem. Phys.* **39**, 3463 (1963).

[62] O'Connor and Nace, *J. Am. Chem. Soc.* **75**, 2118 (1953).

[63] Barton, Head, and Williams, *J. Chem. Soc.* **1953**, 1715.

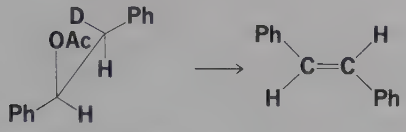
[64] Curtin and Kellom, *J. Am. Chem. Soc.* **75**, 6011 (1953); also see Skell and Hall, *J. Am. Chem. Soc.* **86**, 1557 (1964).



(reaction **7-3**)

erythro (one of the pair)

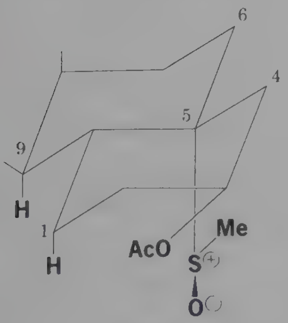
34



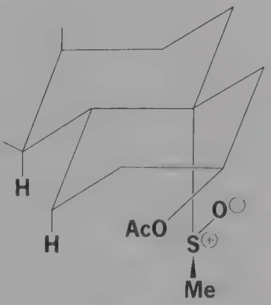
threo (one of the pair)

35

by 5% (instead of 26%) is that there is an isotope effect. The other example involves a pair of steroid molecules. In 3β-acetoxy-(R)-5α-methylsulfinylcholestane (**36** shows rings *A* and *B* of this compound) and in 3β-acetoxy-(S)-5α-methylsulfinylcholestane (**37**: rings *A* and *B*), the *only* difference is the configuration of oxygen and methyl about the sulfur. Yet pyrolysis of **36** gave only elimination to the 4-side (86% 4-ene), while **37** gave predominant elimination to the 6-side (65% 5-ene and 20% 4-ene).[65] Models show that interference from the 1- and 9-hydrogens causes the two groups on the sulfur to lie *in front of* it with respect to the rings, rather than behind it. Since the sulfur is asymmetric, this means that in **36** the oxygen is near the 4-hydrogen while in **37** it is near the 6-hydrogen. Both experiments are compatible only with cis elimination.



36



37

(reaction **7-13**)

2. Some of these reactions have been shown to exhibit negative entropies of activation, indicating that the molecules are more restricted in geometry in the transition state than they are in the starting compound.[62]

The ion-pair mechanism predicts the intermediacy of carbonium ions. Since suitable carbonium ions are known to rearrange (Chapter 18), the finding of rearrangement in pyrolysis reactions is strong evidence for the ion-pair mechanism. Pyrolysis of neopentyl chloride gave 75% HCl (despite the fact that no direct elimination is possible) and a mixture of methylbutenes (which must arise from rearrangement).[66] Rearrangements have also been found on pyrolysis of bornyl and isobornyl chlorides.[67] Further evidence for the ion-pair mechanism is that the relative rates with halide leaving groups are $I > Br > Cl$, which is in the correct order for an ionization mechanism.[68]

---

[65] Jones and Saeed, *Proc. Chem. Soc.* **1964,** 81.

Where a mechanism is on the carbanion–Ei–ion-pair spectrum seems to depend mostly on the leaving group. When this is bromide, all available evidence suggests that the mechanism is well over to the ion-pair side, and the same probably holds true for chloride and iodide. Besides the rearrangement evidence already mentioned, there is the fact that cis elimination has never been demonstrated for halides. Furthermore, an obvious way to study which bond breaks first is to measure the effects of substituents on the rate.[69] Rate ratios for pyrolysis of some alkyl bromides at 320° are: ethyl bromide, 1; isopropyl bromide, 280; *tert*-butyl bromide, 78,000. Also, α-phenylethyl bromide had about the same rate as *tert*-butyl bromide. On the other hand β-phenylethyl bromide was only slightly faster than ethyl bromide. This indicates that C—Br cleavage was much more important in the transition state than C—H cleavage, since the incipient carbonium ion was stabilized by α-alkyl and α-aryl substitution, while there was no incipient carbanion to be stabilized by β-aryl substitution. C_2D_5Br reacted about half as fast as C_2H_5Br,[70] and this isotope effect was taken as evidence that the C—H bond was cleaving in the rate-determining step and that the mechanism was therefore Ei, but this could also be a *secondary* isotope effect on the C—Br cleavage, and in the face of the other evidence the latter interpretation seems more likely. For chlorides the rate ratios were less,[71] and for esters much less,[72] though still in the same order, so that these reactions are closer to a pure Ei mechanism, but still on the ion-pair side of it. Other evidence for a greater initial C—O cleavage with esters is that a series of 1-arylethyl acetates followed σ^+ rather than σ, showing carbonium-ion character at the 1-position.[73] Cleavage of xanthates (reaction **7-4**), the Cope reaction (**7-8**), and reaction **7-7** are probably very close to straight Ei mechanisms.

The third type of pyrolysis mechanism is completely different from the others and involves free radicals. Initiation occurs by pyrolytic homolytic cleavage. The remaining steps may vary, and a few are shown:

---

[66] Maccoll and Swinbourne, *J. Chem. Soc.* **1964**, 149.

[67] Bicknell and Maccoll, *Chem. Ind. (London)* **1961**, 1912.

[68] Maccoll, Ref. 1, pp. 215–216.

[69] For reviews of this approach, see Maccoll, Ref. 1, and Maccoll, in "Theoretical Organic Chemistry, The Kekulé Symposium," pp. 230–249, Butterworth Scientific Publications, London, 1959; also see Green, Maccoll, and Thomas, *J. Chem. Soc.* **1960**, 184.

[70] Blades, *Can. J. Chem.* **36**, 1043 (1958).

[71] Herndon, Sullivan, Henley, and Manion, *J. Am. Chem. Soc.* **86**, 5691 (1964), report a rate order for a series of chlorides that is not exactly the same as the S_N1 rate order, but is similar. Also see Hoffmann and Maccoll, *J. Am. Chem. Soc.* **87**, 3774 (1965).

[72] For example, see Scheer, Kooyman, and Sixma, *Rec. trav. chim.* **82**, 1123 (1963).

[73] Taylor, Smith, and Wetzel, *J. Am. Chem. Soc.* **84**, 4817 (1962); Smith, Jones, and Brown, *J. Org. Chem.* **28**, 403 (1963).

Initiation: $R_2CHCH_2X \longrightarrow R_2CHCH_2\cdot + X\cdot$

Propagation: $R_2CHCH_2X + X\cdot \longrightarrow R_2\underset{\cdot}{C}CH_2X + HX$

$R_2\underset{\cdot}{C}CH_2X \longrightarrow R_2C{=}CH_2 + X\cdot$

Termination (disproportionation):

$2R_2\underset{\cdot}{C}CH_2X \longrightarrow R_2C{=}CH_2 + R_2CXCH_2X$

Free-radical mechanisms are mostly found in pyrolyses of polyhalides and of primary monohalides,[74] though they have been postulated in pyrolysis of certain esters too.[75] Much less is known about these mechanisms, and we shall not consider them further except to say that, when some trans elimination is found in a pyrolytic process, to that extent either an ion-pair or a free-radical mechanism is occurring. In many cases it has not been determined which. Free-radical eliminations in solution are also known but are rare.[76]

Orientation in Pyrolytic Eliminations. As in the E1-E2-E1cB mechanistic spectrum, Bredt's rule applies; and if there is a double bond present, a conjugated system will be preferred, if sterically possible (p. 738). Apart from these considerations, the following statements may be made for Ei eliminations:

1. In the absence of considerations mentioned below, orientation is statistical and is determined by the number of β hydrogens available (therefore *Hofmann's rule* is followed). For example, *sec*-butyl acetate gives 55 to 62% 1-butene and 38 to 45% 2-butene,[77] which is close to the 3:2 distribution predicted by the number of hydrogens available.[78]
2. A cis β hydrogen is required. Therefore in cyclic systems, if there is a cis hydrogen on only one side, the double bond will go that way. However, when there is a six-member transition state, this does not necessarily mean that the leaving groups must be cis to each other, since such transition states need not be completely coplanar. If the leaving group is axial, then the hydrogen obviously must be equatorial (and consequently cis to the leaving group), since the transition state cannot be realized when the groups are both axial. But if the leaving group is equatorial, then it can form a transition state with a β hydrogen which is either axial (hence cis) or equatorial (hence trans). Thus **38**, in which the leaving group is most likely axial, does not form a double bond in the direction of the carbethoxyl group, even though that would be conjugated, because there is no equatorial hydrogen at that side. Instead it gives 100% **39**.[79] On the other hand, **40**, with an

---

[74] For example, Barton and Howlett, *J. Chem. Soc.* **1949**, 155, 165.

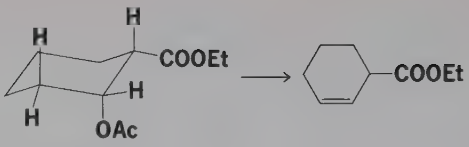
[75] For example, see Rummens, *Rec. trav. chim.* **83**, 901 (1964); Louw and Kooyman, *Rec. trav. chim.* **84**, 1511 (1965).

[76] For an example, see Kampmeier, Geer, Meskin, and D'Silva, *J. Am. Chem. Soc.* **88**, 1257 (1966).

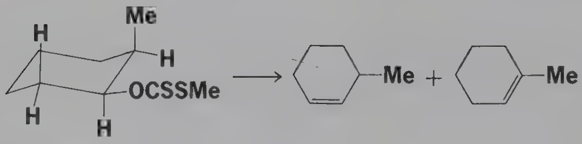
[77] Froemsdorf, Collins, Hammond, and DePuy, *J. Am. Chem. Soc.* **81**, 643 (1959); Haag and Pines, *J. Org. Chem.* **24**, 877 (1959).

[78] DePuy and King, Ref. 60, have tables showing the product distribution for many cases.

[79] Bailey and Baylouny, *J. Am. Chem. Soc.* **81**, 2126 (1959).



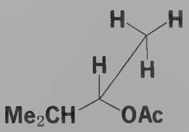
38 **39** (reaction **7-3**)



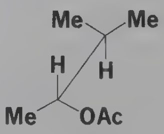
40 (reaction **7-4**)

equatorial leaving group, gives about 50% of each olefin, even though, for elimination to the 1-ene, the leaving group must go off with a trans hydrogen.[80]

3. In open-chain systems, if there is a β hydrogen, there is always a conformation in which it can be cis to the leaving group. However, there may be an eclipsing effect. For example, $Me_2CHCHMeOAc$ gave 80% $Me_2CHCH{=}CH_2$ and 20% $Me_2C{=}CHMe$.[77] Of the two transition states, the one which leads to the larger amount of olefin (**41**) is less eclipsed than the other (**42**). Of course this is a small effect, since a statistical distribution would give a 75:25 ratio, but it is probably real, since it is in the direction away from olefin stability (Zaitsev's rule), and the products from other acetates are in the same direction.



41



42

4. In some cases, especially with cyclic compounds, the more stable olefin forms, and Zaitsev's rule applies. For example, menthyl acetate gives 35% of the Hofmann product and 65% of the Zaitsev, even though a cis β hydrogen is present on both sides and the statistical distribution is the other way. It may be that this is because an ion-pair mechanism is taking over here.[81]

For ion-pair eliminations the data are scantier, but the Zaitsev rule seems to apply, as would be expected for a carbonium-ion mechanism. However, it may be that the most stable product is being formed in at least some cases by rearrangement (since there is usually HX present) of the original product (reaction **2-2**, p. 453).

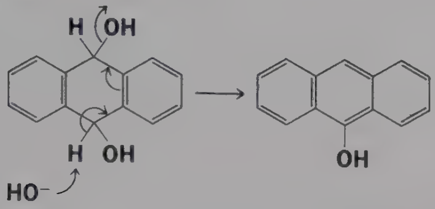
[80] Botteron and Shulman, *J. Org. Chem.* **27**, 2007 (1962).

[81] It has been postulated that this Zaitsev orientation in ester pyrolysis is an *indication* of an ion-pair mechanism. For example, see Rutherford and Fung, *Can. J. Chem.* **42**, 2657 (1964).

1,4 Conjugate Eliminations. 1,4 eliminations of the type

$$H{-}C{-}C{=}C{-}C{-}X \longrightarrow C{=}C{-}C{=}C$$

are much rarer than conjugate additions (Chapter 15), but some examples are known. One such is[82]



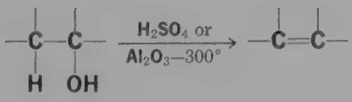
REACTIONS

First we shall consider reactions in which a C=C or a C≡C bond is formed. From a synthetic point of view, the most important reactions for the formation of double bonds are **7-1** (usually by an E1 mechanism), **7-6, 7-14,** and **7-22** (usually by an E2 mechanism), and **7-3, 7-4,** and **7-8** (usually by an Ei mechanism). The only synthetically important method for the formation of triple bonds is **7-14.** In the second section we treat reactions in which C≡N bonds are formed, and then finally eliminations to give C=O bonds and diazoalkanes.

Reactions in Which C=C and C≡C Bonds Are Formed

A. Reactions in which hydrogen is removed from one side. In reactions **7-1** to **7-5** the other leaving atom is oxygen. In reactions **7-6** to **7-11** it is nitrogen. For reactions in which hydrogen is removed from both sides, see reactions **9-1** to **9-7** (pp. 859–867).

7-1 Dehydration of alcohols



$$\underset{H}{-\overset{|}{C}}-\underset{OH}{\overset{|}{C}}- \xrightarrow[Al_2O_3-300^\circ]{H_2SO_4\text{ or}} -\overset{|}{C}=\overset{|}{C}-$$

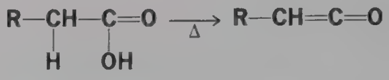
Dehydration of alcohols may be accomplished in several ways. H_2SO_4 and H_3PO_4 are common reagents, but in many cases these lead to rearrangement products and to ether formation (reaction **0-20,** p. 317). If the alcohol can be evaporated, then vapor-phase elimination over Al_2O_3 is an excellent method, since side reactions are greatly reduced. This method has even been applied to such high-molecular-weight alcohols as 1-dodecanol.[83] Another method of avoiding side reactions is the conversion of alcohols to esters, and the pyrolysis of these (reactions **7-3** to **7-5**). The ease of dehydration increases with α branching, and tertiary alcohols are dehydrated so easily with even a trace of acid, that it sometimes happens even when the investigator desires otherwise. It may also be recalled that the initial alcohol products of many base-catalyzed condensations dehydrate spontaneously (Chapter 16) because the new double bond can be in conjugation with one already there. Many other dehydrating agents have been used on occasion: P_2O_5, I_2, $ZnCl_2$, and phthalic anhydride, among others. With nearly all reagents, dehydration follows Zaitsev's rule. An exception involves the passage of hot alcohol vapors over thorium oxide at 350 to 450°, under which conditions Hofmann's rule is followed,[84] and the mechanism is probably different.

---

[82] Cristol, Barasch, and Tieman, *J. Am. Chem. Soc.* **77,** 583 (1955).

[83] Spitzin, Michailenko, and Pirogowa, *J. prakt. Chem.* [4] **25,** 160 (1964).

Carboxylic acids may be dehydrated by pyrolysis, with the product being a ketene:

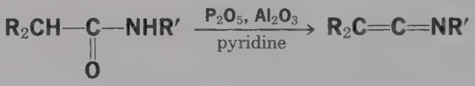


$$\mathrm{R{-}\underset{\displaystyle H}{\underset{|}{C}}H{-}\underset{\displaystyle OH}{\underset{|}{C}}{=}O \xrightarrow[\Delta]{} R{-}CH{=}C{=}O}$$

Ketene itself is commercially prepared in this manner. In a similar reaction, carbon suboxide is produced by heating malonic acid with P_2O_5:

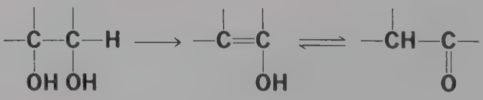
$$\mathrm{HOOC{-}CH_2{-}COOH \longrightarrow O{=}C{=}C{=}C{=}O}$$

Analogously, amides may be dehydrated with P_2O_5, pyridine, and Al_2O_3, to give ketenimines:[85]



$$\mathrm{R_2CH{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}NHR' \xrightarrow[\text{pyridine}]{P_2O_5,\ Al_2O_3} R_2C{=}C{=}NR'}$$

There is no way in which dehydration of alcohols may be used to prepare triple bonds: *gem*-diols and vinyl alcohols do not exist, and *vic*-diols give either conjugated dienes or lose only one mole of water to give an aldehyde or ketone:



$$\mathrm{{-}\underset{\displaystyle OH}{\underset{|}{\overset{|}{C}}}{-}\underset{\displaystyle OH}{\underset{|}{\overset{|}{C}}}{-}H \longrightarrow {-}\overset{|}{C}{=}\underset{\displaystyle OH}{\underset{|}{\overset{|}{C}}} \rightleftharpoons {-}\overset{|}{C}H{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}}$$

When proton acids catalyze alcohol dehydration, the mechanism is E1.[86] The principal process involves conversion of ROH to ROH_2^+ and cleavage of the latter to R^+ and H_2O (this process is not generally called E1cA, though it might be so called, by analogy to S_N1cA, p. 290), though with some acids a secondary process probably involves conversion of the alcohol to an inorganic ester and ionization of *this* (illustrated for H_2SO_4):

$$\mathrm{ROH \xrightarrow{H_2SO_4} ROSO_2OH \longrightarrow R^+ + HSO_4^-}$$

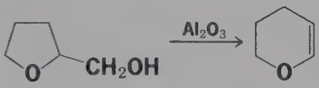
---

[84] Lundeen and Van Hoozer, *J. Am. Chem. Soc.* **85**, 2180 (1963).

[85] Stevens and Singhal, *J. Org. Chem.* **29**, 34 (1964).

[86] For a review, see Banthorpe, Ref. 1, pp. 145–158.

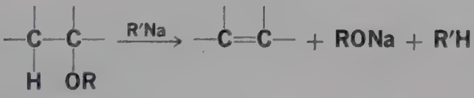
With anhydrides, such as P_2O_5 or phthalic anhydride, it is likely that an ester is formed, and the leaving group is the conjugate base of the corresponding acid. In these cases the mechanism may be E1 or E2. The mechanism with Al_2O_3 has been studied extensively but is poorly understood. It is likely that here too the alcohol is converted to some kind of aluminate ester by the Al_2O_3,[87] though there are often acidic impurities in the Al_2O_3, which can produce ROH_2^+. It has been shown that not only is ethylene produced directly from ethanol (over Al_2O_3) but that some ethylene arises from diethyl ether formed as an intermediate.[88] In some cases, rearrangements occur even with Al_2O_3, for example,[89]



Dehydration of alcohols has also been accomplished by treating the *alkoxide* form of the alcohol with bromoform.[90] A mechanism involving a carbene intermediate has been suggested.

OS **I**, 15, 183, 226, 280, 345, 430, 473, 475; **II**, 12, 368, 408, 606; **III**, 22, 204, 237, 312, 313, 353, 560, 729, 786; **IV**, 130, 444, 771; **40**, 14. No attempt has been made to list olefin-forming dehydrations accompanying condensations or rearrangements.

7-2 Cleavage of ethers to olefins



$$-\underset{\displaystyle H}{\overset{|}{\underset{|}{C}}}-\underset{\displaystyle OR}{\overset{|}{\underset{|}{C}}}- \xrightarrow{R'Na} -\overset{|}{C}=\overset{|}{C}- + RONa + R'H$$

Olefins may be formed by the treatment of ethers with very strong bases, such as alkylsodium or alkyllithium compounds or sodium amide,[91] though there are usually side reactions too. The reaction is aided by electron-withdrawing groups in the β position, and, for example, $EtOCH_2CH(COOEt)_2$ may be converted to $CH_2{=}C(COOEt)_2$ without any base at all, but simply on heating.[92] *tert*-Butyl ethers are cleaved more easily than others. Several mechanisms are possible for the elimination. In many cases the mechanism is probably E1cB, or on the E1cB side of the mechanistic spectrum, since the base required is so strong, but it has been shown (by the use of $PhCD_2OEt$) that $PhCH_2OEt$ reacts by the five-membered Ei mechanism:[93]

---

[87] Pines and Haag, *J. Am. Chem. Soc.* **83**, 2847 (1961).

[88] Balandin, Isaguliants, Popov, Derbentsev, and Vinogradov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1958**, 218.

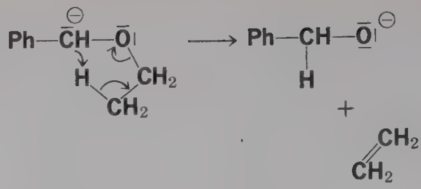
[89] *Org. Syn.* **III**, 276.

[90] Skell and Starer, *J. Am. Chem. Soc.* **81**, 4117 (1959).

[91] For a review, see Köbrich, *Angew. Chem. Intern. Ed. Engl.* **1**, 382–399 (1962), p. 389.

[92] *Org. Syn.* **IV**, 298.

[93] Letsinger and Pollart, *J. Am. Chem. Soc.* **78**, 6079 (1956).

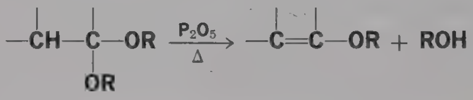


Still another possible mechanism involves carbene formation:

$$R_2CHOR' \xrightarrow{\text{base}} R_2\overset{\ominus}{\bar{C}}OR' \longrightarrow R_2\bar{C} + OR^-$$

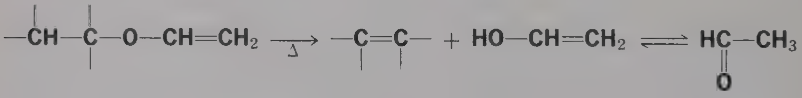
The carbene may then rearrange to an olefin (p. 165) or undergo any of the other carbene reactions. Most of the side reactions in base treatment of olefins arise from this pathway. However, if an alkali metal is involved, side reactions may also arise from reduction of the olefin.

Ethers have also been converted to olefins and alcohols by passing vapors over hot P_2O_5 or Al_2O_3 (this method is similar to reaction **7-1**), but this is not a general reaction. However, acetals are conveniently converted to vinyl ethers in this manner:



$$-\overset{|}{C}H-\underset{OR}{\overset{|}{\underset{|}{C}}}-OR \xrightarrow[\Delta]{P_2O_5} -\overset{|}{C}=\overset{|}{C}-OR + ROH$$

Vinyl ethers may be pyrolyzed to olefins and aldehydes in a manner similar to that of reaction **7-3**:

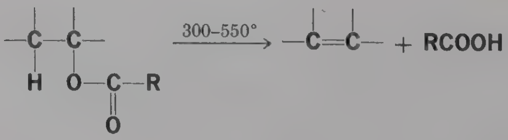


$$-\overset{|}{C}H-\overset{|}{\underset{|}{C}}-O-CH=CH_2 \xrightarrow[\Delta]{} -\underset{|}{C}=\underset{|}{C}- + HO-CH=CH_2 \rightleftharpoons \underset{\underset{O}{\|}}{HC}-CH_3$$

The mechanism is probably similar to that of reaction **7-3.**

OS **IV,** 298, 404; **42,** 14; **43,** 55.

7-3 Pyrolysis of esters of carboxylic acids



$$-\overset{|}{\underset{H}{\underset{|}{C}}}-\overset{|}{\underset{O-\underset{\underset{O}{\|}}{C}-R}{\underset{|}{C}}}- \xrightarrow{300\text{–}550°} -\overset{|}{C}=\overset{|}{C}- + RCOOH$$

Esters in which the alkyl group has a β hydrogen may be pyrolyzed, most often in the gas phase, to give the corresponding acid and an olefin.[94] No solvent is required. Since rearrangement and other side reactions are few, the reaction is synthetically very useful and is often carried out as an indirect

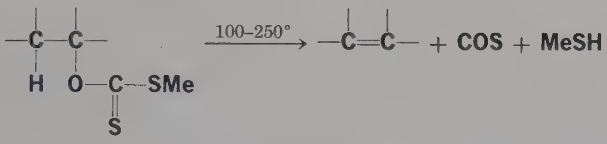
[94] For a review, see DePuy and King, *Chem. Rev.* **60,** 431–458 (1960), pp. 432–444.

method of accomplishing reaction **7-1**. The yields are excellent, and the work-up is easy. Many olefins have been prepared in this manner. For higher olefins (above about C_{10}) a better method is to pyrolyze the *alcohol* in the presence of acetic anhydride.[95]

The mechanism is Ei (see p. 747). Lactones may be pyrolyzed to give unsaturated acids, provided that the six-membered transition state required for Ei reactions is available. Amides give a similar reaction but require higher temperatures.

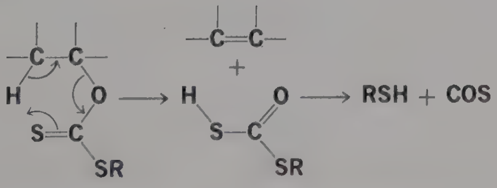
OS **III,** 30; **IV,** 746; **43,** 17.

7-4 The Chugaev reaction



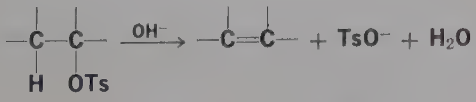
$$-\overset{|}{\underset{\underset{\text{H}}{|}}{\text{C}}}-\overset{|}{\underset{\underset{\text{O}-\underset{\underset{\text{S}}{\|}}{\text{C}}-\text{SMe}}{|}}{\text{C}}}- \xrightarrow{100\text{–}250^\circ} -\overset{|}{\text{C}}=\overset{|}{\text{C}}- + \text{COS} + \text{MeSH}$$

Methyl xanthates are prepared by treatment of alcohols with NaOH and CS_2 to give RO—CS—SNa, followed by treatment of this with methyl iodide. Pyrolysis of the xanthate to give the olefin, COS, and the mercaptan is called the *Chugaev reaction.*[96] The reaction is thus, like reaction **7-3**, an indirect method of accomplishing reaction **7-1**. Elimination is easier with xanthates than with ordinary esters, and the temperatures required are lower, which is advantageous because possible isomerization of the resulting olefin is minimized. The Chugaev reaction is used even more often than reaction **7-3**. The mechanism is Ei, similar to that of reaction **7-3**. For a time there was doubt as to which sulfur atom closed the ring, but now there is much evidence, including the study of ^{34}S and ^{13}C isotope effects, to show that it is the C═S sulfur:[97]



The mechanism is thus exactly analogous to that of reaction **7-3**.

7-5 Decomposition of other esters



$$-\overset{|}{\underset{\underset{\text{H}}{|}}{\text{C}}}-\overset{|}{\underset{\underset{\text{OTs}}{|}}{\text{C}}}- \xrightarrow{\text{OH}^-} -\overset{|}{\text{C}}=\overset{|}{\text{C}}- + \text{TsO}^- + \text{H}_2\text{O}$$

---

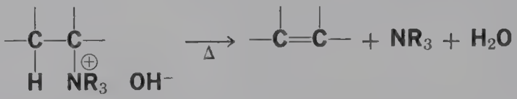
[95] Aubrey, Barnatt, and Gerrard, *Chem. Ind.* (*London*) **1965**, 681.

[96] For reviews, see Ref. 94, pp. 444–448; Nace, *Org. Reactions* **12**, 57–100 (1962).

[97] Bader and Bourns, *Can. J. Chem.* **39**, 348 (1961).

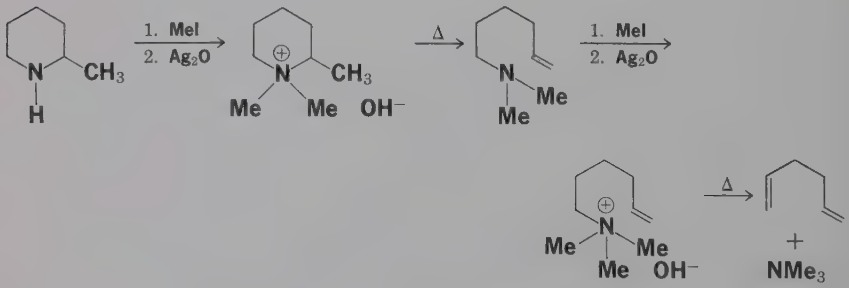
Several types of inorganic esters may be cleaved to olefins by treatment with bases. Esters of sulfuric, sulfurous, and other acids undergo elimination in solution by E1 or E2 mechanisms, as do tosylates and other esters of sulfonic acids. Borates may be pyrolyzed similarly as in reaction **7-3**. High yields of olefins are obtained by heating arylsulfonates in such solvents as dimethyl sulfoxide or dimethylformamide.[98]

7-6 Cleavage of quaternary ammonium hydroxides



$$-\underset{\displaystyle H}{\overset{|}{C}}-\underset{\displaystyle \overset{\oplus}{NR_3}}{\overset{|}{C}}-\quad OH^- \xrightarrow[\Delta]{} -\overset{|}{C}=\overset{|}{C}- + NR_3 + H_2O$$

Cleavage of quaternary ammonium hydroxides is the final step of the process known as *Hofmann exhaustive methylation,* or *Hofmann degradation.*[99] In the first step a primary, secondary, or tertiary amine is treated with enough methyl iodide to convert it to the quaternary ammonium iodide (reaction **0-44**, p. 331). In the second step the iodide is converted to the hydroxide by treatment with silver oxide. In the cleavage step an aqueous or alcoholic solution of the hydroxide is heated, usually above 100°. The reaction has not been used a great deal as a synthetic tool for synthesizing olefins, although some cyclic olefins are best prepared in this way. The principal importance of the method, especially in earlier years, has been for structural determination of unknown amines. The reaction has been extremely useful, especially in the alkaloid field. In many of these compounds the nitrogen is in a ring, or even at a ring junction, and in such cases the olefin still contains nitrogen and repetitions of the process are required to remove the nitrogen completely, for example,



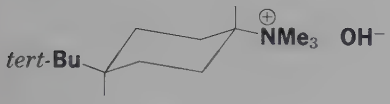
A side reaction involves nucleophilic substitution to give an alcohol ($R_4N^+ \quad OH^- \longrightarrow ROH + R_3N$) instead of the normal elimination, but this seldom causes trouble. However, when none of the four groups on the nitrogen has a β hydrogen, then substitution is the only reaction possible.

---

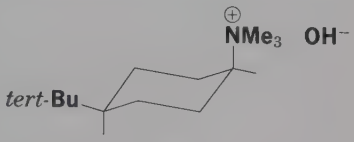
[98] Nace, *J. Am. Chem. Soc.* **81**, 5428 (1959).

[99] For reviews, see Cope and Trumbull, *Org. Reactions* **11**, 317–493 (1960); Bentley, in Bentley, "Elucidation of Structures by Physical and Chemical Methods" (vol. XI of Weissberger, "Technique of Organic Chemistry"), pt. 2, pp. 751–769, Interscience Publishers, Inc., New York, 1963.

On heating of $Me_4N^+ \quad OH^-$ in water, methanol is obtained, though without a solvent, the product is not methanol but dimethyl ether.[100] When a β hydrogen *is* present, then substitution is enhanced at the expense of elimination if one of the R groups is aryl.[101] Substitution is also enhanced when the only β hydrogens in the molecule are present in such positions that it is not possible (or not easily possible) for any of them to be in the anti-periplanar conformation with the nitrogen (p. 728). For example, *trans*-4-*tert*-butylcyclohexyltrimethylammonium hydroxide (**43**), in which the trimethylamino group is in the equatorial position (the axial position is of considerably higher energy, owing to the bulk of the two groups) and consequently cannot easily assume an anti-periplanar conformation with a β hydrogen, gave 100% MeOH when subjected to heat, while the cis isomer, in which about 50% of the molecules exist in the conformation shown in **44**, gave 92% elimination and 8% substitution.[102] However, cis elimination (from a syn-periplanar conformation) has also been demonstrated, in the case of 2-norbornyltrimethylammonium hydroxide.[102a]

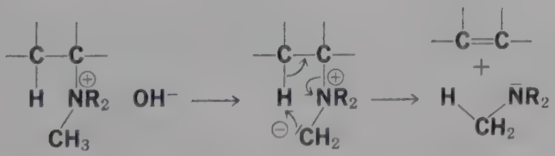


43



44

The mechanism is usually E2, so that Hofmann's rule is normally obeyed, although under some conditions E1 elimination (and hence Zaitsev's rule) has been observed. Zaitsev orientation is sometimes found (in cyclic systems) even where the mechanism is unquestionably E2.[103] In such cases there is probably a considerable amount of E1 character. In certain cases, where the geometry of the system is very unfavorable to trans elimination, a five-membered Ei mechanism, similar to that in reaction **7-7**, has been shown to operate. That is, the OH^- in these cases does not attract the β hydrogen, but instead removes one of the methyl hydrogens:



The obvious way to distinguish between this mechanism and the ordinary E2 mechanism is by use of deuterium labeling. For example, if the reaction is carried out on a quaternary hydroxide deuterated on the β-carbon

---

[100] Musker, *J. Am. Chem. Soc.* **86**, 960 (1964); Tanaka, Dunning, and Carter, *J. Org. Chem.* **31**, 3431 (1966).

[101] Archer and Booth, *J. Chem. Soc.* **1963**, 322.

[102] Curtin, Stolow, and Maya, *J. Am. Chem. Soc.* **81**, 3330 (1959).

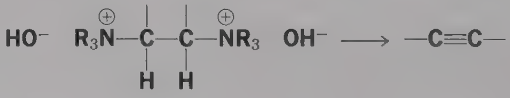
[102a] Coke and Cooke, Ref. 12.

[103] For example, see Ledger, Smith, and McKenna, *Tetrahedron* **20**, 2413 (1964).

($R_2CDCH_2NMe_3^+$ OH^-), then the fate of the deuterium indicates the mechanism. If the E2 mechanism is operating, then the trimethylamine produced should contain no deuterium (which would be found only in the water). But if the mechanism is Ei, then the amine would contain deuterium. In the case of the highly hindered compound $(Me_3C)_2CDCH_2NMe_3^+$ OH^-, the deuterium did appear in the amine, demonstrating an Ei mechanism for this case.[104] However, with simpler compounds, the mechanism is E2, as shown by the fact that here the amine was deuterium-free.[105] In the case of eliminations to give medium rings (8- to 14-membered), quaternary ammonium salts give cis cycloolefins by the E2 mechanism and trans cycloolefins by the Ei mechanism, as shown by rate and deuterium-labeling studies.[106]

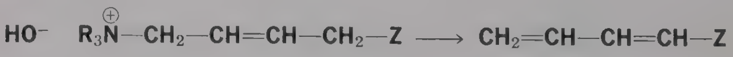
When the nitrogen bears more than one group possessing a β hydrogen, which group cleaves? The Hofmann rule says that *within* a group the hydrogen on the least alkylated carbon cleaves. This tendency is also carried over to the choice of which group cleaves: thus ethyl with three β hydrogens cleaves more readily than any longer *n*-alkyl group, all of which have two β hydrogens. "The β-hydrogen is removed most readily if it is located on a methyl group, next from RCH_2, and least readily from R_2CH."[107] In fact, the Hofmann rule as first stated[108] in 1851 applied only to which group cleaved, and not to the orientation within a group; the latter could not have been specified by him in 1851, since the structural theory of organic compounds was not formulated until 1857–1860. Of course, the Hofmann rule (applied to which group cleaves *or* to orientation within a group) is superseded by the requirement of a trans β hydrogen and by conjugation possibilities. Thus $PhCH_2CH_2NMe_2Et^+$ OH^- gives mostly styrene instead of ethylene.

Triple bonds have been prepared by pyrolysis of 1,2-bis salts:[109]



$$HO^- \quad R_3\overset{\oplus}{N}-\underset{H}{\overset{|}{C}}-\underset{H}{\overset{|}{C}}-\overset{\oplus}{N}R_3 \quad OH^- \longrightarrow -C\equiv C-$$

If a double bond is β,γ to the amino group, it is possible to get 1,4 elimination, especially if there is a group Z (such as phenyl) which stabilizes the new double bond:[110]



$$HO^- \quad R_3\overset{\oplus}{N}-CH_2-CH=CH-CH_2-Z \longrightarrow CH_2=CH-CH=CH-Z$$

OS **IV**, 980; **41**, 49. Also see OS **40**, 52; **42**, 83.

---

[104] Cope and Mehta, *J. Am. Chem. Soc.* **85**, 1949 (1963).

[105] Cope, LeBel, Moore, and Moore, *J. Am. Chem. Soc.* **83**, 3861 (1961).

[106] Sicher, Závada, and Krupička, *Tetrahedron Letters* **1966**, 1619; Závada, Svoboda, and Sicher, *Tetrahedron Letters* **1966**, 1627.

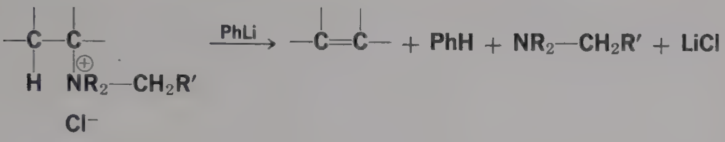
[107] Cope and Trumbull, Ref. 99, p. 348.

[108] Hofmann, *Ann.* **78**, 253 (1851).

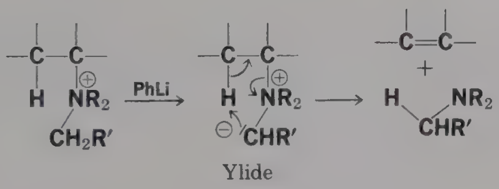
[109] For a review, see Franke, Ziegenbein, and Meister, *Angew. Chem.* **72**, 391–400 (1960), pp. 397–398.

[110] Babayan, Indzhikyan, Grigoryan, and Minasyan, *J. Gen. Chem. USSR* **33**, 1720 (1963).

7-7 Cleavage of quaternary ammonium salts with strong bases

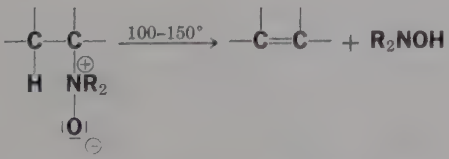


When quaternary ammonium halides are treated with organometallic compounds (usually phenyllithium), an elimination occurs which is similar in products, though not in mechanism, to reaction **7-6**.[111] This represents an alternative to reaction **7-6** and is done on the quaternary ammonium halide, so that it is not necessary to convert this to the hydroxide. The mechanism is Ei:



An α' hydrogen is obviously necessary so that the ylide can be formed. This type of mechanism is called α'-β-elimination, since a β hydrogen is removed by the α' carbon. The mechanism has been confirmed by labeling experiments similar to those described at reaction **7-6**,[112] and by isolation of the intermediate ylides.[113] Only organometallic compounds, and not other strong bases, effect the reaction. An important synthetic difference between this and most instances of reaction **7-6** is that cis elimination is observed here and trans elimination in reaction **7-6**, so that products of opposite configuration are formed when the olefin exhibits cis-trans isomerism.

7-8 Cleavage of amine oxides



Cleavage of amine oxides is called the *Cope reaction* (not to be confused with the Cope *rearrangement,* reaction **8-26**, p. 834). It is an alternative to reactions **7-6** and **7-7**.[114] The reaction is usually performed with a mixture of amine and oxidizing agent (see reaction **9-25**, p. 886) without isolation of the amine oxide. Because of the mild conditions side reactions are few, and the olefins do not usually rearrange. The reaction is thus very useful for the preparation of many olefins. However, it does not open six-membered rings containing hetero nitrogen, although it does open rings of five and seven to ten members.[115] The reaction can be carried out at room temperature in dry dimethyl sulfoxide or tetrahydrofuran.[116] The mechanism is the five-membered Ei mechanism:

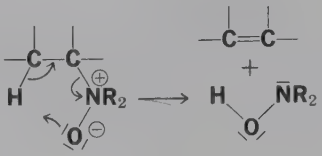
---

[111] For reviews, see Wittig, *Experientia* **14**, 393 (1958); Cope and Trumbull, Ref. 99, pp. 373–374.

[112] Weygand, Daniel, and Simon, *Chem. Ber.* **91**, 1691 (1958).

[113] Wittig and Polster, *Ann.* **612**, 102 (1958); Wittig and Burger, *Ann.* **632**, 85 (1960).

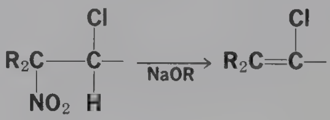
[114] For reviews, see Cope and Trumbull, Ref. 99, pp. 361–370, and Ref. 94, pp. 448–451.



and all evidence indicates that the transition state must be planar. Deviations from planarity as in reaction **7-3** (see p. 747) are not found here, and indeed this is why six-membered heterocyclic nitrogen compounds do not react. Because of the stereoselectivity of this reaction and because of the lack of rearrangement of the products, it is useful for the formation of trans cycloolefins (eight-membered and higher).

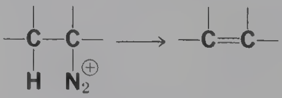
OS **IV,** 612.

7-9 Cleavage of α-chloro tertiary nitro compounds



α-Chloro olefins may be prepared by the treatment of α-chloro tertiary nitro compounds with sodium alkoxides.[117]

7-10 Olefins from aliphatic diazonium salts



The treatment of aliphatic amines with nitrous acid is not a useful method for the preparation of olefins, any more than it is for the preparation of alcohols (reaction **0-5**, p. 305), although some olefin is usually formed in such reactions.

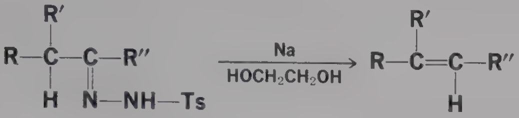
---

[115] Cope and LeBel, *J. Am. Chem. Soc.* **82,** 4656 (1960); Cope, Ciganek, Howell, and Schweizer, *J. Am. Chem. Soc.* **82,** 4663 (1960).

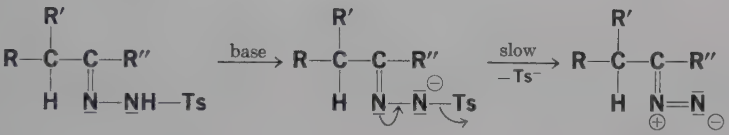
[116] Cram, Sahyun, and Knox, *J. Am. Chem. Soc.* **84,** 1734 (1962).

[117] Dornow and Müller, *Chem. Ber.* **93,** 41 (1960).

7-11 Decomposition of toluene-*p*-sulfonylhydrazones

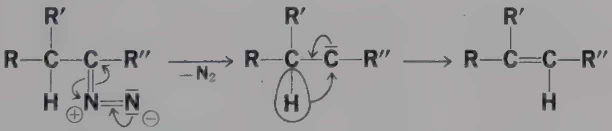


When the tosylhydrazone of an aldehyde or ketone is treated with sodium in ethylene glycol, an olefin results, the reaction being formally an elimination accompanied by a shift of hydrogen.[118] The reaction, known as the *Bamford-Stevens reaction,* has been applied to tosylhydrazones of many aldehydes and ketones. In the absence of protic solvents the mechanism is carbenoid. The first two steps involve the formation of a diazo compound (**45**):



45

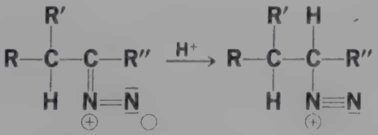
This has been demonstrated by running the reaction on compounds without a β hydrogen, in which cases the diazo compound may be isolated.[119] The diazo compound then loses nitrogen, and a hydride shift occurs, giving the olefin:



45 **46**

There are indications that these two steps are simultaneous, so that no free carbene (**46**) is involved. Thus, camphene formed in this reaction was optically active,[118] and side reactions expected from a free carbene were absent.[119] However, there is other evidence[120] that a free carbene *is* an intermediate.

In the presence of protic solvents, the carbenoid pathway is not followed. The first two steps are the same, and **45** is produced. But before it can lose nitrogen, it gains a proton, producing a diazonium ion:



45

---

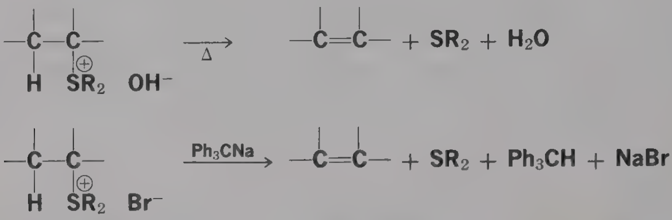
[118] Bamford and Stevens, *J. Chem. Soc.* **1952,** 4735.
[119] Powell and Whiting, *Tetrahedron* **7,** 305 (1959), **12,** 168 (1961).
[120] Closs, Closs, and Böll, *J. Am. Chem. Soc.* **85,** 3796 (1963).

which may then react by a normal E1 or E2 reaction to give the olefin (reaction **7-10**).[121]

The bis tosylhydrazone of benzil gives diphenylacetylene, when treated with HgO.[122]

OS **IV**, 377.

7-12 Cleavage of sulfonium compounds

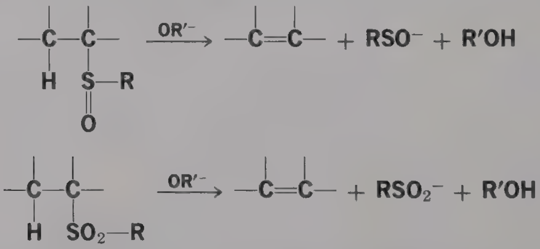


$$\text{H}-\text{C}-\text{C}-\overset{\oplus}{\text{SR}_2}\ \text{OH}^- \xrightarrow[\Delta]{} -\text{C}=\text{C}- + \text{SR}_2 + \text{H}_2\text{O}$$

$$\text{H}-\text{C}-\text{C}-\overset{\oplus}{\text{SR}_2}\ \text{Br}^- \xrightarrow{\text{Ph}_3\text{CNa}} -\text{C}=\text{C}- + \text{SR}_2 + \text{Ph}_3\text{CH} + \text{NaBr}$$

Sulfonium compounds undergo elimination similar to that of their ammonium counterparts (reactions **7-6** and **7-7**) in scope and in mechanism. The decomposition by heat of sulfonium hydroxides has been known for many years. The ylide reaction was discovered more recently.[123] Neither is important synthetically.

7-13 Cleavage of sulfones and sulfoxides



$$\text{H}-\text{C}-\text{C}-\text{S(=O)}-\text{R} \xrightarrow{\text{OR}'^-} -\text{C}=\text{C}- + \text{RSO}^- + \text{R}'\text{OH}$$

$$\text{H}-\text{C}-\text{C}-\text{SO}_2-\text{R} \xrightarrow{\text{OR}'^-} -\text{C}=\text{C}- + \text{RSO}_2^- + \text{R}'\text{OH}$$

Sulfones and sulfoxides with a β hydrogen undergo elimination upon treatment with an alkoxide or, for sulfones, even with OH^-.[124] In mechanism, these reactions belong on the E1-E2-E1cB spectrum.[125] Although the leaving groups are uncharged, the orientation follows Hofmann's rule and not Zaitsev's. Sulfoxides (but not sulfones) also undergo elimination upon pyrolysis at about 80° in a manner analogous to reaction **7-8.** The mechanism is also analogous, being the five-membered Ei mechanism with cis elimination.[126] Sulfides and disulfides also undergo elimination when heated with KOH in the polar aprotic solvent hexamethylphosphoramide.[127]

---

[121] DePuy and Froemsdorf, *J. Am. Chem. Soc.* **82,** 634 (1960).

[122] *Org. Syn.* **IV**, 377.

[123] Franzen and Mertz, *Chem. Ber.* **93,** 2819 (1960).

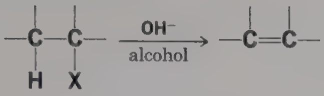
[124] Hofmann, Wallace, Argabright, and Schriesheim, *Chem. Ind.* (*London*) **1963,** 1234.

[125] Hofmann, Wallace, and Schriesheim, *J. Am. Chem. Soc.* **86,** 1561 (1964).

[126] Kingsbury and Cram, *J. Am. Chem. Soc.* **82,** 1810 (1960); Walling and Bollyky, *J. Org. Chem.* **29,** 2699 (1964); Entwhistle and Johnstone, *Chem. Commun.* **1965,** 29.

[127] Wallace, Hofmann, and Schriesheim, *Chem. Ind.* (*London*) **1965,** 1768.

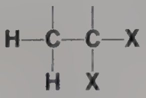
7-14 Dehydrohalogenation of alkyl halides



$$-\underset{H}{\overset{|}{C}}-\underset{X}{\overset{|}{C}}- \xrightarrow[\text{alcohol}]{OH^-} -\overset{|}{C}=\overset{|}{C}-$$

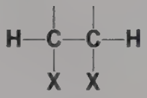
The elimination of HX from an alkyl halide is a very general reaction and can be accomplished with chlorides, fluorides,[128] bromides, and iodides. Hot alcoholic KOH is the most frequently used base, though stronger bases (OR^-, NH_2^-, etc.) or weaker ones (e.g., amines) are used where warranted. Tertiary halides undergo the reaction most easily. The eliminations follow Zaitsev's rule except for a few cases where steric effects are important (for an example, see p. 741).

This reaction is by far the most important way of introducing a triple bond into a molecule.[129] This may be accomplished with substrates of the types **47** to **49**. The most commonly used base for triple-bond formation is $NaNH_2$. This base causes 1-alkynes to predominate (where possible),



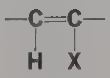
$$H-\underset{H}{\overset{|}{C}}-\underset{X}{\overset{|}{C}}-X$$

47



$$H-\underset{X}{\overset{|}{C}}-\underset{X}{\overset{|}{C}}-H$$

48



$$-\underset{H}{C}=\underset{X}{C}-$$

49

because it forms the salt of the alkyne, shifting any equilibrium between 1- and 2-alkynes. When the base is OH^- or OR^-, the equilibrium tends to be shifted to the internal alkyne, which is thermodynamically more stable. If another hydrogen is suitably located (for example, $-\overset{|}{C}H-CX_2-CH_2-$), then allene formation can compete, though alkynes are usually more stable.[129a]

Dehydrohalogenation is generally carried out in solution, with a base, and the mechanism is usually E2, though the E1 mechanism has been demonstrated in some cases. However, elimination of HX may also be accomplished by pyrolysis of the halide, in which case the mechanism is the ion-pair or the Ei mechanism (p. 747), or in some instances the free-radical mechanism (p. 750). Pyrolysis is normally performed without a catalyst at about 400°. Less mechanistic work has been done on pyrolysis with a catalyst (usually $CaCl_2$ or CaO) but these reactions have been shown to be nonstereospecific,[130] so that either a carbonium-ion or a free-radical intermediate is probable. It has been shown that, when a very strong base is used in solution, an α-elimination mechanism through the carbene may compete with the normal E2 mechanism. This was shown by the treatment of $CH_3CH_2CH_2CD_2Cl$

---

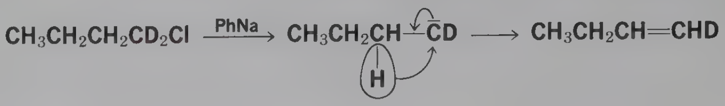
[128] For example, see Nield, Stephens, and Tatlow, *J. Chem. Soc.* **1959**, 159, 166.

[129] For reviews, see Jacobs, *Org. Reactions* **5**, 1–78 (1949), pp. 1–25; Ref. 109, pp. 391–397; Köbrich, Ref. 1, pp. 50–53.

[129a] For a review of allene formation, see Taylor, *Chem. Rev.* **67**, 317–359 (1967), p. 321–322.

[130] Noller, Hantsche, and Andréu, *Angew. Chem. Intern. Ed. Engl.* **3**, 584 (1964); Andréu, Heunisch, Schmitz, and Noller, *Z. Naturforsch.* **19b**, 649 (1964).

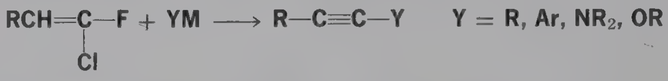
with phenylsodium; the product contained $CH_3CH_2CH{=}CDH$, which arises from



$$CH_3CH_2CH_2CD_2Cl \xrightarrow{PhNa} CH_3CH_2\underset{H}{CH}{-}\overset{-}{C}D \longrightarrow CH_3CH_2CH{=}CHD$$

and there was more of the former than of $CH_3CH_2CH{=}CD_2$, the normal E2 product.[131]

A combination elimination and substitution reaction has been used to synthesize alkynes. In this reaction a compound $RCH{=}CFCl$ is treated with YM, where M is a metal and Y may be alkyl, aryl, NR_2, or OR:

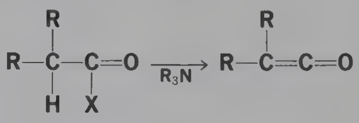


$$RCH{=}\underset{Cl}{C}{-}F + YM \longrightarrow R{-}C{\equiv}C{-}Y \qquad Y = R, Ar, NR_2, OR$$

Alkynes, ynamines, and acetylenic ethers may be prepared in this manner.[132]

OS **I**, 191, 205, 209, 438; **II**, 10, 17, 515; **III**, 125, 209, 270, 350, 506, 623, 731, 785; **IV**, 128, 162, 398, 404, 555, 608, 616, 683, 711, 727, 748, 755, 763, 851, 969; **45**, 86.

7-15 Dehydrohalogenation of acyl halides



$$R{-}\underset{H}{\overset{R}{C}}{-}\underset{X}{C}{=}O \xrightarrow[R_3N]{} R{-}\overset{R}{C}{=}C{=}O$$

Ketenes may be prepared by treatment of acyl halides with tertiary amines, but the scope of the reaction is fairly limited.[133] If at least one R is hydrogen, only ketene dimers are isolated.

OS **IV**, 560.

7-16 Elimination of boranes

$$(R_2CH{-}CH_2)_3B + 3\ \text{1-decene} \rightleftharpoons 3R_2C{=}CH_2 + [CH_3(CH_2)_8CH_2]_3B$$

Trialkylboranes are formed from an olefin and B_2H_6 (reaction **5-13**, p. 599). When the resulting borane is treated with another olefin, an exchange reaction occurs.[134] This is an equilibrium process, which may be shifted by distillation of the lower-boiling olefin. The reaction is useful for shifting a double bond in the opposite direction from that done by the normal isomerization methods (reaction **2-2**, p. 453). This cannot be accomplished simply by treatment of a borane such as **51** with an olefin, for elimination in this reaction follows Zaitsev's rule: it is in the direction of the most stable olefin, and the product would be **50**, and not **53**. However, if it is desired to convert **50** to **53**, this can be accomplished by converting **50** to **51**, isomerizing

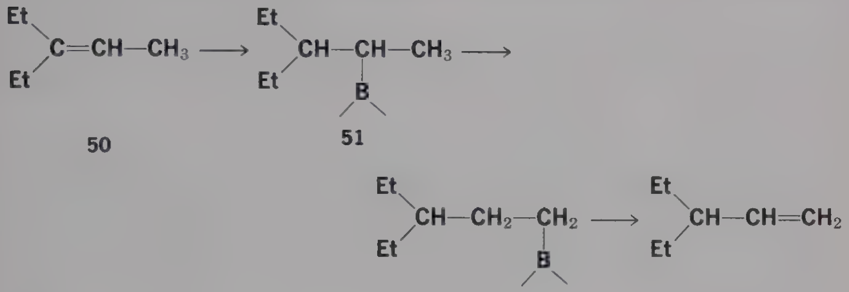
---

[131] Friedman and Berger, *J. Am. Chem. Soc.* **83**, 492, 500 (1961).

[132] Viehe, *Angew. Chem. Intern. Ed. Engl.* **2**, 477 (1963).

[133] For a review, see Hanford and Sauer, *Org. Reactions* **3**, 108–140 (1946), pp. 124–126.

[134] Brown and Bhatt, *J. Am. Chem. Soc.* **88**, 1440 (1966); Brown, "Hydroboration," pp. 150–160, W. A. Benjamin, Inc., New York, 1962.



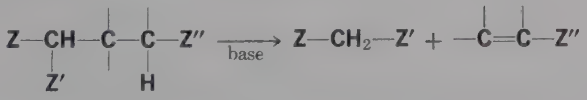
50 **51** **52** **53**

51 to **52** (reaction **8-12**, p. 814), and then subjecting **52** to the exchange reaction with a higher-boiling olefin, e.g., 1-decene, whereupon **53** is produced. In the usual isomerizations (reaction **2-2**, p. 453), **53** could be isomerized to **50**, but not the other way around. The reactions **51** → **52** and **52** → **53** proceed essentially without rearrangement. The mechanism is probably the reverse of diborane addition (reaction **5-13**, p. 599).

A similar reaction, but irreversible, has been demonstrated for alkynes:[135]

$$(R_2CH{-}CH_2)_3B + R'C{\equiv}CR' \longrightarrow 3R_2C{=}CH_2 + (R'CH{=}CR')_3B$$

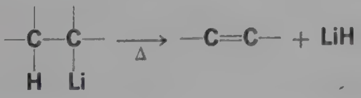
7-17 Reversal of the Michael reaction



$$Z{-}\underset{Z'}{CH}{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{H}{C}}{-}Z'' \xrightarrow[\text{base}]{} Z{-}CH_2{-}Z' + {-}\overset{|}{C}{=}\overset{|}{C}{-}Z''$$

Olefins may be formed upon base cleavage of Michael adducts. (See reaction **5-15**, p. 604. Z is defined on p. 568.) In some cases cleavage occurs simply on heating, without basic catalysis.

7-18 Pyrolysis of alkali-metal organometallic compounds



$$-\overset{|}{\underset{H}{C}}-\overset{|}{\underset{Li}{C}}- \xrightarrow[\Delta]{} -C{=}C- + LiH$$

Solid lithium hydride and an olefin may be obtained by heating alkyllithium compounds which contain a β hydrogen.[136] With *sec*-BuLi the orientation followed Zaitsev's rule, although formation of *cis*-2-butene predominated over formation of the trans isomer.[137] The reaction has also been applied to alkylsodium and alkylpotassium compounds.[138] Grignard reagents gave olefins when thermally decomposed in nonsolvating solvents, e.g., cumene.[139]

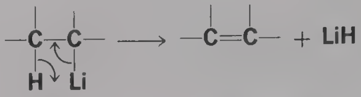
---

[135] Hubert, *J. Chem. Soc.* **1965**, 6669.

[136] Ziegler and Gellert, *Ann.* **567**, 179 (1950).

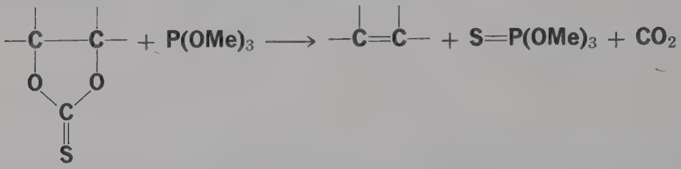
[137] Glaze, Lin, and Felton, *J. Org. Chem.* **30**, 1258 (1965).

The kinetics of the organolithium reaction have been shown to be first order.[140] A possible mechanism is

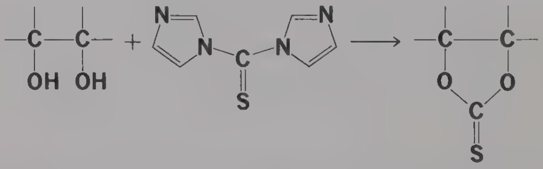


B. Reactions in which neither leaving atom is hydrogen

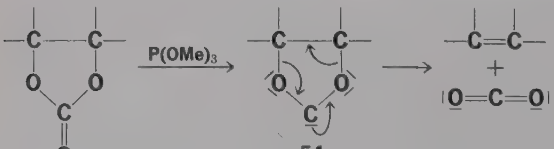
7-19 Cleavage of cyclic thionocarbonates



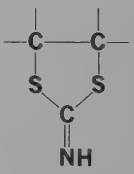
Cyclic thionocarbonates may be cleaved to olefins by treatment with trimethyl phosphite.[141] This is actually a method for removing *vic*-OH groups from a molecule, since the thionocarbonates may be prepared by the treatment of 1,2-glycols with N,N′-thiocarbonyldiimidazole:



The elimination is, of course, cis, so the product is sterically controlled, and olefins which are not sterically favored may be made in this way, in high yield; for example, *cis*-$PhCH_2CH{=}CHCH_2Ph$.[142] This is an example of a reaction which was invented with the idea that a postulated mechanism would take place. That is, Corey and Winter thought it likely that trimethyl phosphite would remove sulfur from the thionocarbonate to give the carbene **54**, and that this would go on to form CO_2 and an olefin:



54



55

---

[138] For example, see Finnegan, *Chem. Ind. (London)* **1962**, 895, *Tetrahedron Letters* **1963**, 851.

[139] Zakharkin, Okhlobystin, and Strunin, *J. Organometal. Chem.* **4**, 349 (1965).

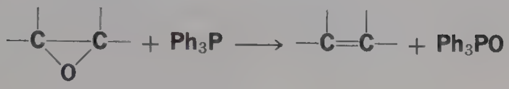
[140] Finnegan and Kutta, *J. Org. Chem.* **30**, 4138 (1965).

[141] Corey and Winter, *J. Am. Chem. Soc.* **85**, 2677 (1963).

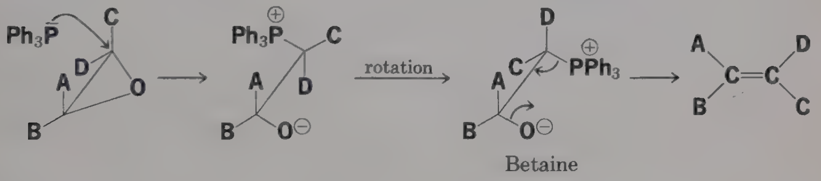
[142] Corey, Carey, and Winter, *J. Am. Chem. Soc.* **87**, 934 (1965).

This is apparently just what happened. The reaction was also performed on the analogous **55.**[142]

7-20 The conversion of epoxides to olefins

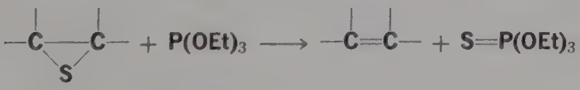


Epoxides may be converted to olefins by treatment with triphenylphosphine[143] or triethyl phosphite [P(OEt)$_3$].[144] The first step of the mechanism is nucleophilic substitution (reaction **0-49,** p. 334), followed by a four-center elimination. Since inversion accompanies the substitution, the overall elimination is trans; that is, if two groups A and C are cis in the epoxide, they will be trans in the olefin:



For another method of preparing the betaine, and hence olefins, see the Wittig reaction (**6-45,** p. 702). Olefins have also been obtained from epoxides by reaction with NaI-NaOAc-Zn-AcOH.[145] This method is actually a variation of reaction **7-24,** since iodohydrins are intermediates.

7-21 The conversion of episulfides to olefins



Episulfides may be converted to olefins in a reaction similar in appearance to reaction **7-20.**[146] However, in this case the elimination is cis, so that the mechanism could not be the same as that of reaction **7-20.** The phosphite attacks not the carbon, but the sulfur. Other reagents which convert episulfides to olefins are phenyllithium, lithium aluminum hydride[147] (this compound behaves quite differently with epoxides, see reaction **0-76,** p. 350), and methyl iodide. The latter mechanism is complex and involves several nucleophilic substitutions:

---

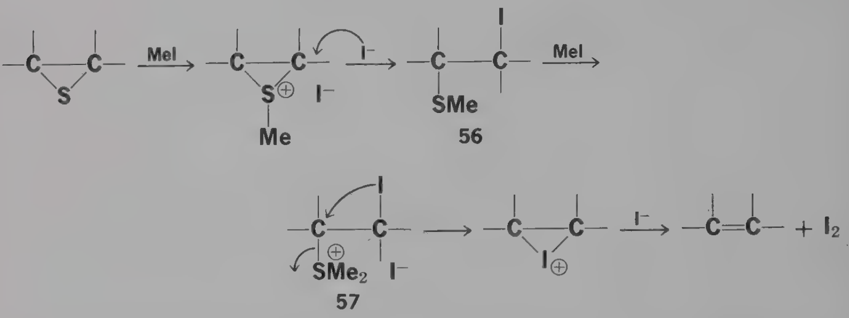
[143] Wittig and Haag, *Chem. Ber.* **88,** 1654 (1955).

[144] Scott, *J. Org. Chem.* **22,** 1118 (1957).

[145] Cornforth, Cornforth, and Mathew, *J. Chem. Soc.* **1959,** 112.

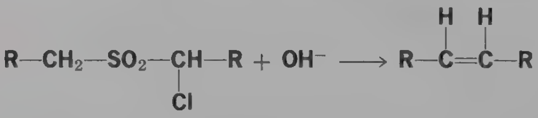
[146] Neureiter and Bordwell, *J. Am. Chem. Soc.* **81,** 578 (1959); Davis, *J. Org. Chem.* **23,** 1767 (1957).

[147] Lightner and Djerassi, *Chem. Ind. (London)* **1962,** 1236.



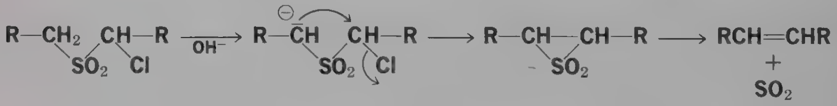
This mechanism was demonstrated by the isolation of intermediates corresponding to **56** and **57** when the reaction was carried out with methyl bromide, and the conversion of these to olefin with iodide ion.[148] The intermediates from methyl iodide treatment were too reactive for isolation.

When α-halo sulfones are treated with base, they give olefins:

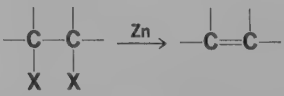


$$R-CH_2-SO_2-\underset{\displaystyle Cl}{\underset{|}{CH}}-R + OH^- \longrightarrow R-\overset{\displaystyle H}{\overset{|}{C}}=\overset{\displaystyle H}{\overset{|}{C}}-R$$

The reaction is quite general for α-halo sulfones with an α′ hydrogen. The mechanism involves formation of an episulfone, and then elimination of SO_2:[149]



7-22 Dehalogenation of vicinal dihalides



$$-\underset{\displaystyle X}{\underset{|}{\overset{|}{C}}}-\underset{\displaystyle X}{\underset{|}{\overset{|}{C}}}- \xrightarrow{Zn} -\overset{|}{C}=\overset{|}{C}-$$

Dehalogenation has been accomplished with many reagents, the most common being zinc, magnesium, and iodide ion. Among reagents used less frequently have been phenyllithium, phenylhydrazine, and lithium aluminum hydride.[150] Although the reaction usually gives good yields, it is not very useful, because the best way to prepare *vic*-dihalides is by the addition of halogen to a double bond (reaction **5-22**, p. 610). However, the two reactions are sometimes used to purify olefins. One useful feature of this reaction is that there is no doubt about the *position* of the new double bond, so that it can be used to give double bonds exactly where they are wanted. For example, allenes, which are not easily prepared by other methods, can be prepared from $X{-}C{-}CX_2{-}C{-}X$ or $X{-}C{-}CX{=}C{-}$ systems.[150a] Cumulenes have been obtained from 1,4 elimination:

---

[148] Culvenor, Davies, and Heath, *J. Chem. Soc.* **1949**, 282; Helmkamp and Pettitt, *J. Org. Chem.* **29**, 3258 (1964).

[149] Bordwell and Cooper, *J. Am. Chem. Soc.* **73**, 5187 (1951); Neureiter, *J. Am. Chem. Soc.* **88**, 558 (1966).

[150] For a list of reagents, see King and Pews, *Can. J. Chem.* **42**, 1294 (1964).

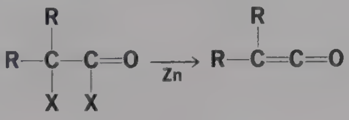
$$BrCH_2{-}C{\equiv}C{-}CH_2Br + Zn \longrightarrow CH_2{=}C{=}C{=}CH_2$$

Triple bonds may be prepared from $X{-}C{=}C{-}X$ or $X_2C{-}CX_2$ systems, but availability considerations are even more extreme here.

The reaction may be carried out for any combination of halogens except where one is fluorine. The mechanism with iodide ion is probably E2, since trans stereospecific is observed (p. 729). When the reagent is zinc, trans stereospecificity has been observed in some cases,[151] but not in others.[152]

OS **III,** 526, 531; **IV,** 195, 268; **42,** 12, 44; **45,** 22; **46,** 93. Also see OS **IV,** 877, 914, 964.

7-23 Dehalogenation of α-halo acyl halides

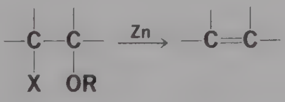


$$R_2CX{-}C(X){=}O \xrightarrow[Zn]{} R_2C{=}C{=}O$$

Ketenes may be prepared by dehalogenation of α-halo acyl halides, analogously to reaction **7-22.** The reaction gives good results when the two R groups are aryl or alkyl, but not when either one is hydrogen.

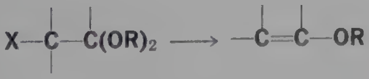
OS **IV,** 348.

7-24 Elimination of a halogen and a hetero group



$$-\underset{X}{\overset{|}{C}}-\underset{OR}{\overset{|}{C}}- \xrightarrow{Zn} -\overset{|}{C}{=}\overset{|}{C}-$$

The elimination of OR and halogen from β-halo ethers is called the *Boord reaction.* It may be carried out with zinc, magnesium, or sodium. The yields are high and the reaction is of broad scope. β-Halo acetals yield vinyl ethers:



$$X{-}\underset{|}{\overset{|}{C}}{-}\overset{|}{C}(OR)_2 \longrightarrow -\overset{|}{C}{=}\overset{|}{C}{-}OR$$

[150a] For a review, see Ref. 129*a*, pp. 319–320.

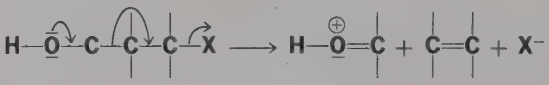
[151] House and Ro, *J. Am. Chem. Soc.* **80,** 182 (1958).

[152] Stevens and Valicenti, *J. Am. Chem. Soc.* **87,** 838 (1965).

Besides β-halo ethers, the reaction may also be carried out on compounds of the formula $X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}Z$, where X is halogen and Z is OCOR, OTs,[153] NR_2,[154] or SR.[155] Z may also be OH, but then X is limited to Br and I. Like reaction **7-23**, this method ensures that the new double bond will be in a specific position. The fact that magnesium causes elimination in these cases limits the preparation of Grignard reagents from these compounds. It has been shown that treatment of β-halo ethers and esters with zinc gives nonstereospecific elimination,[151] so that the mechanism was not E2. It was postulated that the mechanism is E1cB, because of the poor leaving-group ability of OR and OCOR.

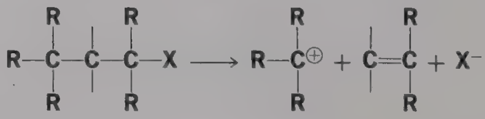
OS **III**, 698; **IV**, 748.

When carbon is the positive leaving group in an elimination reaction, the reaction is called *fragmentation.*[156] These processes occur on substrates of the form $W{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}X$, where X is a normal leaving group (e.g., halogen, OH_2^+, OTs, NR_3, etc.) and W is a positive-carbon leaving group. In most of the cases W is HO—C— or R_2N—C—, so that the positive charge on the carbon atom is stabilized by the unshared pair of the oxygen or nitrogen, e.g.,



The mechanism may be E1 or E2. We shall discuss only a few fragmentations, since many are possible and not much work has been done on most of them. Reactions **7-25** to **7-29** and **7-31** may be considered fragmentations.

7-25 Fragmentation of γ-branched alcohols and halides



When alkyl halides or alcohols with both α and γ branching are subjected to solvolysis, they undergo fragmentation to give an olefin and a carbonium ion. The carbonium ion then undergoes further elimination or substitution, depending on the conditions. This is, of course, an E1 process, with the first step being ionization of the halide or the protonated alcohol. This is another way of saying that carbonium ions of the form $R_3C-\overset{|}{\underset{|}{C}}-\overset{\oplus}{C}R_2$ find it easy to lose a relatively stable R_3C^+ carbonium ion rather than H^+. As expected for a carbonium-ion mechanism, these fragmentations occur to the greatest extent for tertiary substrates, to a smaller extent for secondary, and essentially not at all for primary substrates, even with γ branching, although they have been shown to occur for primary substrates when a very stable carbonium ion (the xanthyl cation) could be expelled:[157]

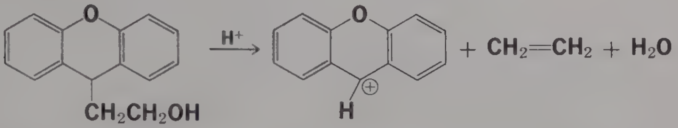
---

[153] Cristol and Rademacher, *J. Am. Chem. Soc.* **81**, 1600 (1959).

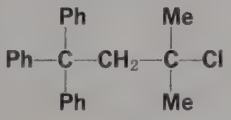
[154] Gurien, *J. Org. Chem.* **28**, 878 (1963).

[155] Amstutz, *J. Org. Chem.* **9**, 310 (1944).

[156] For reviews, see Grob and Schiess, *Angew. Chem. Intern. Ed. Engl.* **6**, 1–15 (1967); Grob, *Bull. Soc. chim. France* **1960**, 1360–1365; Grob, in "Theoretical Organic Chemistry, The Kekulé Symposium," pp. 114–126, Butterworth Scientific Publications, London, 1959.

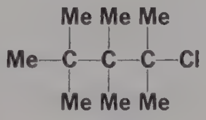


Even with apparently favorable substrates, fragmentation is not always observed. Thus, 2-methyl-4,4,4-triphenyl-2-chlorobutane (**58**) and 2,3,3,4,4-pentamethyl-2-chloropentane (**59**) gave no fragmentation products when solvolyzed in aqueous acetone.[158]



$$Ph-\overset{Ph}{\underset{Ph}{C}}-CH_2-\overset{Me}{\underset{Me}{C}}-Cl$$

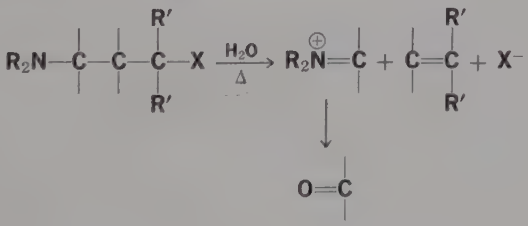
58



$$Me-\overset{Me}{\underset{Me}{C}}-\overset{Me}{\underset{Me}{C}}-\overset{Me}{\underset{Me}{C}}-Cl$$

59

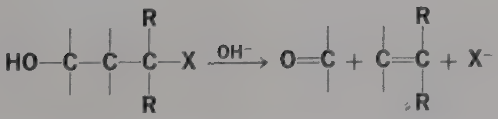
7-26 Fragmentation of γ-amino and γ-hydroxy halides



$$R_2N-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{R'}{\underset{R'}{C}}-X \xrightarrow[\Delta]{H_2O} R_2\overset{\oplus}{N}=\overset{|}{\underset{|}{C}} + \overset{|}{\underset{|}{C}}=\overset{R'}{\underset{R'}{C}} + X^-$$

$$\downarrow$$

$$O=\overset{|}{\underset{|}{C}}$$



$$HO-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{R}{\underset{R}{C}}-X \xrightarrow{OH^-} O=\overset{|}{\underset{|}{C}} + \overset{|}{\underset{|}{C}}=\overset{R}{\underset{R}{C}} + X^-$$

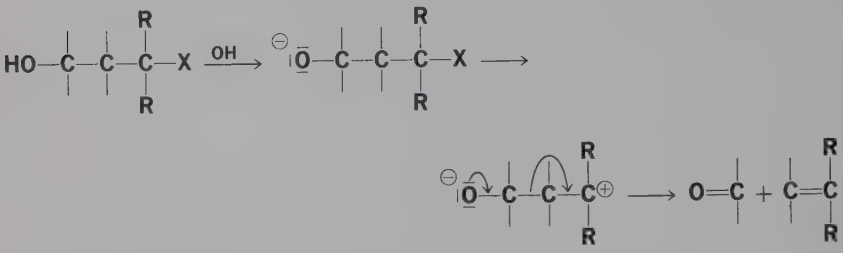
γ-Dialkylamino halides undergo fragmentation when heated with water, to give an olefin and an iminium salt, which under the reaction conditions is hydrolyzed to an aldehyde or ketone (reaction **6-2**, p. 656).[159] γ-Hydroxy halides are fragmented with base. In this instance the base does not play its usual role in elimination reactions, but instead serves to remove a proton from the OH group, enabling the carbon leaving group to come off more easily:

---

[157] Deno and Sachar, *J. Am. Chem. Soc.* **87**, 5120 (1965).

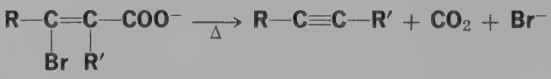
[158] Shiner and Meier, *J. Org. Chem.* **31**, 137 (1966).

[159] Grob and Ostermayer, *Helv. Chim. Acta* **45**, 1119 (1962); Grob, Ostermayer, and Raudenbusch, *Helv. Chim. Acta* **45**, 1672 (1962).



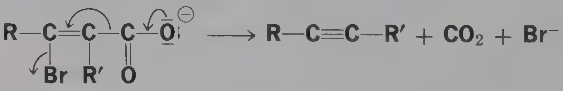
The mechanism of these reactions is probably E1, and the side reactions are similar to those in reaction **7-25.** However, in at least some cases, an E2 mechanism has been shown.[160] γ-Dialkylamino alcohols do not give fragmentation, since for ionization the OH group must be converted to OH_2^+ and this would convert NR_2 to NR_2H^+, which does not have the unshared pair necessary to form the double bond with the carbon.[161]

7-27 Fragmentation of β-halo acrylic acid salts

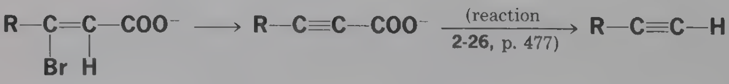


$$R\text{—}\underset{Br}{\underset{|}{C}}\text{=}\underset{R'}{\underset{|}{C}}\text{—}COO^- \xrightarrow[\Delta]{} R\text{—}C\equiv C\text{—}R' + CO_2 + Br^-$$

Salts of β-halo acrylic acids are dehalocarboxylated by heating, to give triple-bond compounds.[162] The elimination is trans, as shown by the fact that *trans*-MeCBr=CMeCOO⁻ reacts at 100°, while the cis isomer does not react. The mechanism is thus probably E2:



When R′ is hydrogen, then another mechanism is possible:



$$R\text{—}\underset{Br}{\underset{|}{C}}\text{=}\underset{H}{\underset{|}{C}}\text{—}COO^- \longrightarrow R\text{—}C\equiv C\text{—}COO^- \xrightarrow[\textbf{2-26},\text{ p. 477)}]{\text{(reaction}} R\text{—}C\equiv C\text{—}H$$

Other leaving groups (for example, OTs) may replace halogen.

A similar cleavage may be effected by base treatment of β-chloroacroleins:[163]

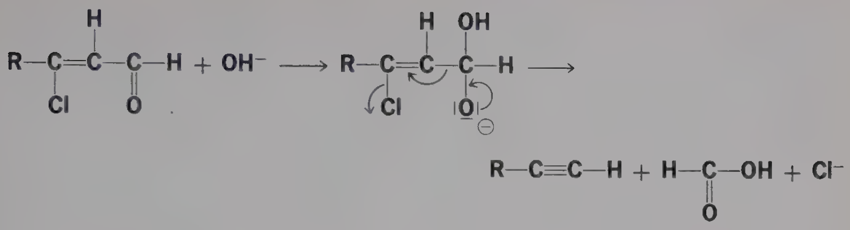
---

[160] Grob and Schwarz, *Helv. Chim. Acta* **47,** 1870 (1964); Brenneisen, Grob, Jackson, and Ohta, *Helv. Chim. Acta* **48,** 146 (1965); D'Arcy, Grob, Kaffenberger, and Krasnobajew, *Helv. Chim. Acta* **49,** 185 (1966).

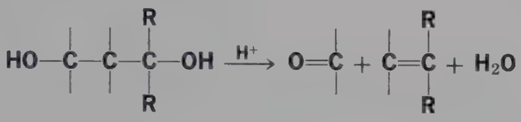
[161] Grob, Hoegerle, and Ohta, *Helv. Chim. Acta* **45,** 1823 (1962).

[162] For a review, see Köbrich, Ref. 1, pp. 54–55.

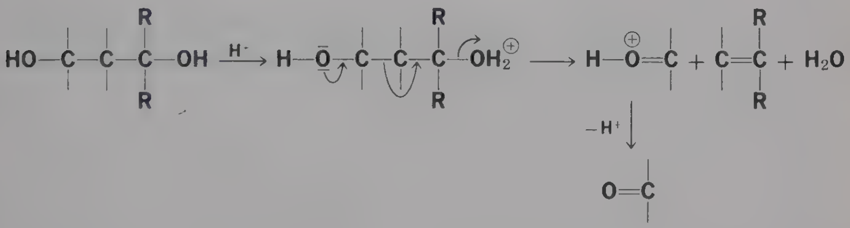
[163] Bodendorf and Mayer, *Chem. Ber.* **98,** 3554 (1965).



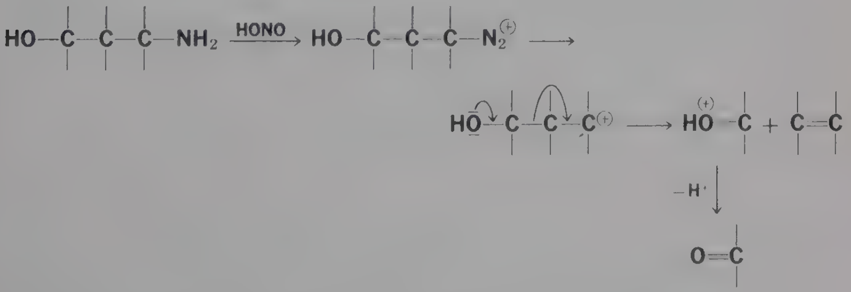
7-28 Fragmentation of 1,3-diols



1,3-Diols in which at least one OH group is tertiary or is located on a carbon which has aryl substituents may be cleaved by acid treatment.[164] At least in some cases the mechanism seems to be E2, since trans elimination is found:[165]



However, in other cases the mechanism is E1. Suitable β-hydroxy acids also give the reaction. As already mentioned (p. 774), γ-dialkylamino alcohols do not give fragmentation, but non-N-substituted γ-amino alcohols do give the reaction, when treated with nitrous acid, and give the same products as from the corresponding 1,3-diol.[166] Here the mechanism is undoubtedly E1:



---

[164] Zimmerman and English, *J. Am. Chem. Soc.* **76,** 2285, 2291, 2294 (1954).

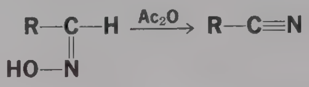
[165] Maggio and English, *J. Am. Chem. Soc.* **83,** 968 (1961).

[166] English and Bliss, *J. Am. Chem. Soc.* **78,** 4057 (1956).

7-29 Reversal of the Diels-Alder reaction may be considered a fragmentation. See reaction **5-34** (p. 626).

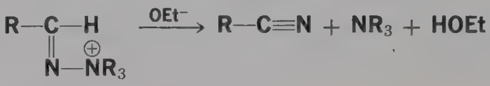
Reactions in Which C≡N Bonds Are Formed

7-30 Dehydration of aldoximes and similar compounds



$$R-\underset{\underset{HO-N}{\|}}{C}-H \xrightarrow{Ac_2O} R-C\equiv N$$

Aldoximes may be dehydrated to nitriles by many dehydrating agents, of which acetic anhydride is the most common. The reaction is most successful when the H and OH are trans. Various alkyl and acyl derivatives of aldoximes, for example, $RCH{=}NOR$, $RCH{=}NOCOR$, $RCH{=}NOSO_2Ar$, etc., also give nitriles, as do chlorimines $RCH{=}NCl$ (the latter with base treatment).[167] Quaternary hydrazonium salts (derived from aldehydes) give nitriles when treated with OEt^-:[168]

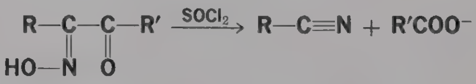


$$R-\underset{\underset{N-\overset{\oplus}{N}R_3}{\|}}{C}-H \xrightarrow{OEt^-} R-C\equiv N + NR_3 + HOEt$$

All of these are methods of converting aldehyde derivatives to nitriles. For the conversion of aldehydes directly to nitriles, without isolation of intermediates, see reaction **6-23** (p. 675).

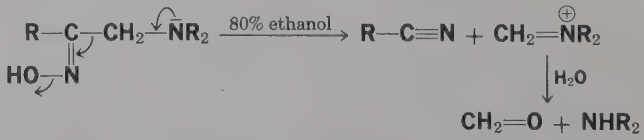
OS **II**, 622; **III**, 690.

7-31 The conversion of ketoximes to nitriles



$$R-\underset{\underset{HO-N}{\|}}{C}-\underset{\underset{O}{\|}}{C}-R' \xrightarrow{SOCl_2} R-C\equiv N + R'COO^-$$

Certain ketoximes may be converted to nitriles by the action of proton or Lewis acids. Among these are oximes of α-diketones (illustrated above), α-keto acids, α-dialkylamino ketones, α-hydroxy ketones, β-keto ethers, and similar compounds.[169] These are fragmentation reactions, analogous to reactions **7-26** and **7-28**. For example, α-dialkylamino ketoximes also give amines and aldehydes or ketones, in addition to nitriles:[170]



$$R-\underset{\underset{HO-N}{\|}}{C}-CH_2-\bar{N}R_2 \xrightarrow{80\%\ \text{ethanol}} R-C\equiv N + CH_2{=}\overset{\oplus}{N}R_2 \xrightarrow{H_2O} CH_2{=}O + NHR_2$$

---

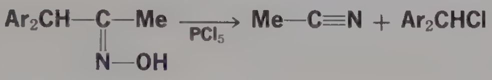
[167] Hauser, Le Maistre, and Rainsford, *J. Am. Chem. Soc.* **57**, 1056 (1935).

[168] Smith and Walker, *J. Org. Chem.* **27**, 4372 (1962); Grandberg, *J. Gen. Chem. USSR* **34**, 570 (1964); Grundon and Scott, *J. Chem. Soc.* **1964**, 5674.

[169] For a more complete list, and references, see Hill, *J. Org. Chem.* **27**, 29 (1962).

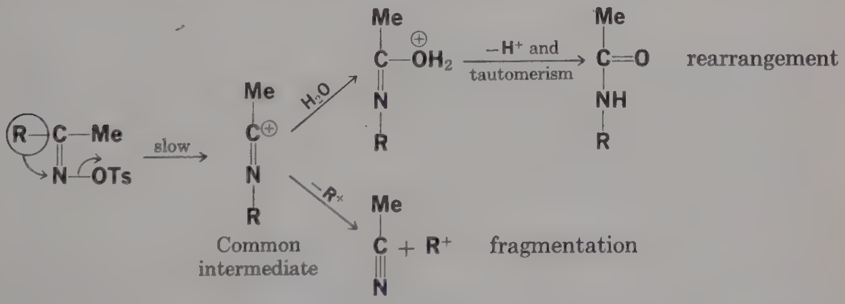
[170] Fischer, Grob, and Renk, *Helv. Chim. Acta* **45**, 2539 (1962); Fischer and Grob, *Helv. Chim. Acta* **46**, 936 (1963).

The reaction which normally occurs upon treatment of a ketoxime with a Lewis or proton acid is the Beckmann rearrangement (reaction **8-19**, p. 821), and fragmentations are considered side reactions, often called "abnormal" or "second-order" Beckmann rearrangements.[171] Obviously the substrates mentioned are much more susceptible to fragmentation than are ordinary ketoximes, since in each case an unshared pair is available to assist in removal of the group cleaving from the carbon. However, fragmentation is a side reaction even with ordinary ketoximes[172] and, in cases where a particularly stable carbonium ion may be cleaved, may be the main reaction:[173]



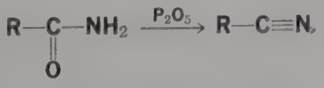
$$\mathrm{Ar_2CH{-}\underset{\underset{\displaystyle N{-}OH}{\|}}{C}{-}Me \xrightarrow[PCl_5]{} Me{-}C{\equiv}N + Ar_2CHCl}$$

There are indications that the mechanism at least in some cases first involves a rearrangement, and then cleavage. The ratio of fragmentation to Beckmann rearrangement of a series of oxime tosylates $\mathrm{R{-}\underset{\underset{\displaystyle NOTs}{\|}}{C}{-}Me}$ was not related to the solvolysis rate but *was* related to the stability of R^+ (as determined by the solvolysis rate of the corresponding RCl), which showed that fragmentation did not take place in the rate-determining step.[174] It may be postulated then that the first step in the fragmentation and in the rearrangement is the same and that this is the rate-determining step. The product is determined in the second step:



However, in other cases it is possible that the fragmentation is a simple E1 or E2 process.[175]

7-32 Dehydration of unsubstituted amides



$$\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}NH_2 \xrightarrow{P_2O_5} R{-}C{\equiv}N}$$

---

[171] See the discussion in Ferris, *J. Org. Chem.* **25,** 12 (1960).

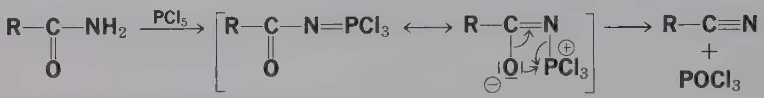
[172] See, for example, Hill and Conley, *J. Am. Chem. Soc.* **82,** 645 (1960).

[173] Hassner and Nash, *Tetrahedron Letters* **1965,** 525.

[174] Grob, Fischer, Raudenbusch, and Zergenyi, *Helv. Chim. Acta* **47,** 1003 (1964).

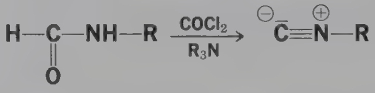
[175] Ahmad and Spenser, *Can. J. Chem.* **39,** 1340 (1961), and Ferris, Johnson, and Gould, *J. Org. Chem.* **25,** 1813 (1960), describe the mechanisms in this manner. However, their results are also compatible with the Grob mechanism.

Unsubstituted amides may be dehydrated to nitriles. Phosphorus pentoxide is the most common dehydrating agent for this reaction, but many others, including $POCl_3$, PCl_5, and $SOCl_2$, have also been used. It is possible to convert an acid to the nitrile, without isolation of the amide, by heating its ammonium salt with the dehydrating agent. The reaction may be formally looked upon as a β-elimination from the enol form of the amide, $\mathrm{R{-}\underset{\underset{\displaystyle OH}{|}}{C}{=}NH}$, in which case it is like reaction **7-30**, except that H and OH have changed places. The mechanism probably *is* through the enol form, with the dehydrating agent forming an ester with the OH group, for example, $\mathrm{R{-}\underset{\underset{\displaystyle OSOCl}{|}}{C}{=}NH}$, which undergoes elimination by the E1 or E2 mechanism.[176] With PCl_5 the mechanism is different, and not through the enol:



OS **II,** 379; **III,** 493, 535, 584, 646, 768; **IV,** 62, 144, 166, 172, 436, 486, 706.

7-33 Conversion of N-alkylformamides to isonitriles



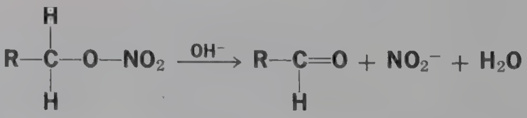
$$\mathrm{H{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}NH{-}R \xrightarrow[R_3N]{COCl_2} \overset{\ominus}{C}{\equiv}\overset{\oplus}{N}{-}R}$$

Isonitriles may be prepared by elimination of water from N-alkylformamides with phosgene and a tertiary amine.[177] Other reagents, among them *para*-toluenesulfonyl chloride in quinoline and phosphorus oxychloride in pyridine, have also been employed.

OS **41,** 13, 101; **46,** 75.

Reactions in Which C=O Bonds Are Formed. Many elimination reactions in which C=O bonds are formed were considered in Chapter 16, along with their more important reverse reactions. Also see reactions **2-26** (p. 477), **2-27** (p. 480), **2-28** (p. 480), and **4-28** (p. 560).

7-34 Alkaline hydrolysis of nitrates



$$\mathrm{R{-}\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}{-}O{-}NO_2 \xrightarrow{OH^-} R{-}\underset{\underset{\displaystyle H}{|}}{C}{=}O + NO_2^- + H_2O}$$

Nitrates of primary or secondary alcohols may be hydrolyzed with base to give aldehydes or ketones,[178] but other reactions compete: hydrolysis to the alcohol (reaction **0-4**, p. 305) and elimination to the olefin (reaction **7-5**). Compounds in which R is aryl give the highest yields. The mechanism is E2.[179] This is an indirect method of oxidation of alcohols to aldehydes or ketones. (See reaction **9-3**, p. 862.)

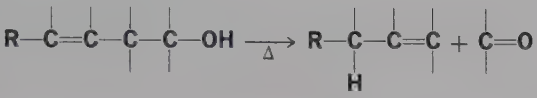
---

[176] Rickborn and Jensen, *J. Org. Chem.* **27**, 4608 (1962).

[177] For a review, see Ugi, Fetzer, Eholzer, Knupfer, and Offermann, *Angew. Chem. Intern. Ed. Engl.* **4**, 472–484 (1965).

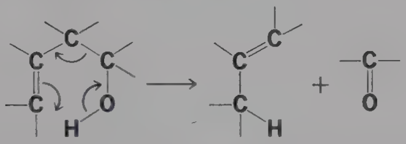
[178] Boschan, Merrow, and Van Dolah, *Chem. Rev.* **55**, 485–510 (1955).

7-35 Pyrolysis of β-hydroxy olefins



$$R-C{=}C-C-C-OH \xrightarrow{\Delta} R-\underset{H}{C}-C{=}C + C{=}O$$

β-Hydroxy olefins are cleaved when pyrolyzed to give olefins and aldehydes or ketones.[180] Olefins produced in this way are quite pure, since there are no side reactions. The mechanism has been shown to be Ei:

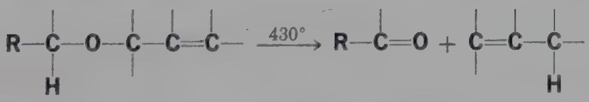


primarily by the observations that the kinetics are first order[181] and that, for ROD, the deuterium appeared in the allylic position of the new olefin.[182]

An example of this reaction is the pyrolysis of ricinoleic acid

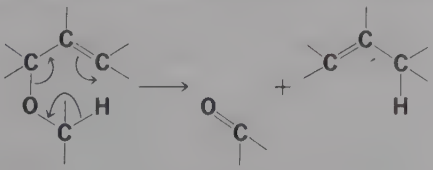
$$CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_7COOH \longrightarrow CH_3(CH_2)_5CHO + CH_2{=}CH(CH_2)_8COOH$$

7-36 Pyrolysis of allyl ethers



$$R-\underset{H}{C}-O-C-C{=}C- \xrightarrow{430°} R-C{=}O + C{=}C-\underset{H}{C}-$$

Pyrolysis of allyl ethers which contain at least one α hydrogen gives olefins and aldehydes or ketones.[183] The reaction is closely related to reaction **7-35**, and the mechanism is also Ei, though not exactly analogous:



---

[179] Buncel and Bourns, *Can. J. Chem.* **38**, 2457 (1960).

[180] Arnold and Smolinsky, *J. Am. Chem. Soc.* **81**, 6443 (1959).

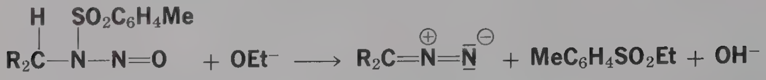
[181] Smith and Yates, *J. Chem. Soc.* **1965**, 7242.

[182] Arnold and Smolinsky, *J. Org. Chem.* **25**, 128 (1960); Smith and Taylor, *Chem. Ind.* (*London*) **1961**, 949.

[183] Cookson and Wallis, *Proc. Chem. Soc.* **1963**, 58.

Reactions in Which N=N Bonds Are Formed

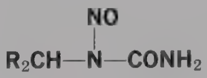
7-37 Eliminations to give diazoalkanes



$$R_2\overset{\overset{H}{|}}{C}{-}\overset{\overset{SO_2C_6H_4Me}{|}}{N}{-}N{=}O + OEt^- \longrightarrow R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{\underline{\bar{N}}} + MeC_6H_4SO_2Et + OH^-$$

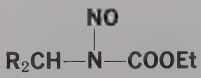
Various N-nitroso-N-alkyl compounds undergo elimination to give diazoalkanes.[184] One of the most convenient methods for the preparation of diazomethane involves base treatment of N-nitroso-N-methyl-*p*-toluenesulfonamide (illustrated above, with R = H).[185] However, other compounds commonly used are (base treatment is required in all cases):

N-nitroso-N-alkylureas



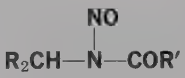
$$R_2CH{-}\overset{\overset{NO}{|}}{N}{-}CONH_2$$

N-nitroso-N-alkylurethans



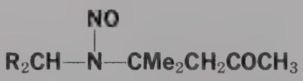
$$R_2CH{-}\overset{\overset{NO}{|}}{N}{-}COOEt$$

N-nitroso-N-alkyl amides



$$R_2CH{-}\overset{\overset{NO}{|}}{N}{-}COR'$$

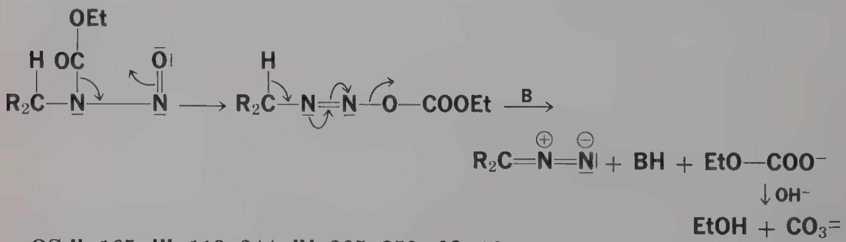
N-nitroso-N-alkyl-4-amino-4-methyl-2-pentanones



$$R_2CH{-}\overset{\overset{NO}{|}}{N}{-}CMe_2CH_2COCH_3$$

All of these compounds may be used to prepare diazomethane, although the sulfonamide, which is commercially available, is most satisfactory. (N-Nitroso-N-methylurethan gives good results but is highly irritating and carcinogenic.) For higher diazoalkanes the preferred substrates are nitrosoalkylurethans.

Most of these reactions probably begin with a 1,3 nitrogen-to-oxygen rearrangement, followed by the actual elimination (illustrated for the urethan):



$$R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{\underline{N}}| + BH + EtO{-}COO^- \xrightarrow{OH^-} EtOH + CO_3^=$$

OS **II,** 165; **III,** 119, 244; **IV,** 225, 250; **40,** 16.

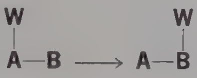
---

[184] For discussions, see Smith, "Open-chain Nitrogen Compounds," vol. 2, especially pp. 257–258, 474–475, W. A. Benjamin, Inc., New York, 1966, and Gutsche, *Org. Reactions* **8,** 364–429 (1954), pp. 389–390.

[185] *Org. Syn.* **IV,** 225, 250.

CHAPTER EIGHTEEN
Rearrangements

In a rearrangement reaction a group moves from one atom to another in the same molecule.[1] Most are migrations from an atom to an adjacent one (called 1,2-shifts)



$$\overset{\mathrm{W}}{\overset{|}{\mathrm{A}}}\text{—}\mathrm{B} \longrightarrow \mathrm{A}\text{—}\overset{\mathrm{W}}{\overset{|}{\mathrm{B}}}$$

but some are over longer distances. The migrating group (W) may be moving with its electron pair (these are called *anionotropic rearrangements*), without its pair (*cationotropic,* or in the case of migrating hydrogen, *prototropic* rearrangements), or with just one electron (free-radical rearrangements). The atom A is called the *migration origin,* and B is the *migration terminus.* However, there are some rearrangements which do not lend themselves to neat categorization in this manner. Among these are those with cyclic transition states (reactions **8-24** to **8-28**).

In any rearrangement we may in principle distinguish between two possible modes of reaction: in one of these the group W becomes completely detached from A and may end up on the B atom of a different molecule (*intermolecular* rearrangement), and in the other W goes from A to B in the *same* molecule (*intramolecular* rearrangement), in which case there must be some continuing tie holding W to the A—B system, preventing it from coming completely free. Strictly speaking, only the intramolecular type fit our definition of a rearrangement, but the general practice, which is followed here, is to include under the title "rearrangement" all net rearrangements whether they are inter- or intramolecular. It is usually not difficult to tell whether a given rearrangement is intramolecular or not. The most common method is the use of *crossover* experiments. In this type of experiment, rearrangement is carried out on a mixture of W—A—B and V—A—C, where V is closely related to W (say, methyl versus ethyl) and B to C. In an intramolecular process only A—B—W and A—C—V will be recovered, but if the reaction is intermolecular, then not only will these two be found, but also A—B—V and A—C—W.

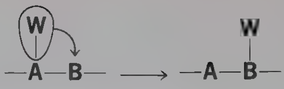
MECHANISMS

Anionotropic Rearrangements.[2] Broadly speaking, such rearrangements consist of three steps, of which the actual migration is the second:

---

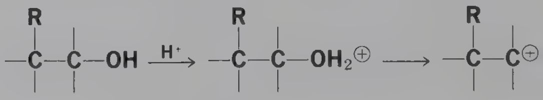
[1] For a treatise, see Mayo, "Molecular Rearrangements," 2 vols., Interscience Publishers, Inc., New York, 1963.

[2] For a review, see Wheland, "Advanced Organic Chemistry," 3d ed., pp. 550–619, John Wiley & Sons, Inc., New York, 1960.



This process is sometimes called the Whitmore 1,2-shift.[3] Since the migrating group carries the electron pair with it, the migration terminus B must have an open sextet. The first step therefore is creation of a system with an open sextet. Such a system may arise in various ways, but two of these are the most important:

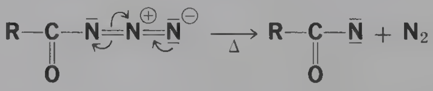
1. *Formation of a carbonium ion.* Carbonium ions may be formed in a number of ways (see p. 140), but one of the most common methods when a rearrangement is desired is the acid treatment of an alcohol:



1

These two steps are, of course, the same as the first two steps of the S_N1cA or the E1 reactions of alcohols.

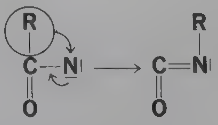
2. *Formation of a nitrene.* The decomposition of acyl azides is one of several ways in which nitrenes are formed:



2

After the migration has taken place, the atom at the migration origin (A) must necessarily have an open sextet. In the third step this atom acquires an octet. In the case of carbonium ions, the most common third steps are combinations with a nucleophile (rearrangement with substitution) and loss of a hydrogen (rearrangement with elimination).

Although we have presented this mechanism as taking place in three steps, and some reactions do take place in this way, in many cases two or all three steps are actually simultaneous. For instance, in the nitrene example above, as the R migrates, an electron pair from the nitrogen moves into the C—N bond to give a stable isocyanate:

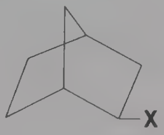


---

[3] It was first postulated by Whitmore, *J. Am. Chem. Soc.* **54**, 3274 (1932).

In this example, the second and third steps are simultaneous. It is also possible for the second and third steps to be simultaneous even when the "third" step involves more than just a simple motion of a pair of electrons. Similarly, there are reactions in which the first two steps are simultaneous; that is, there is no actual formation of a species such as **1** or **2.** In these instances it may be said that R assists in the removal of the leaving group, with migration of R and the removal of the leaving group taking place simultaneously. Such is probably the case in the nitrene reaction mentioned above,[4] so that in this reaction all three steps are concurrent. However, it has been argued that the nitrene is free, at least for a short time.[5] It is not easy to decide this point.

Evidence for this mechanism is that rearrangements of this sort occur under conditions where we have previously encountered carbonium ions: S_N1 conditions, Friedel-Crafts alkylation, etc. Solvolysis of neopentyl bromide leads to rearrangement products, and the rate increases with increasing ionizing power of the solvent but is unaffected by concentration of base,[6] so that the first step is carbonium-ion formation. The same compound under S_N2 conditions gave no rearrangement, but only ordinary substitution, though slowly. Thus with neopentyl bromide, formation of a carbonium ion leads only to rearrangement. Carbonium ions usually rearrange to more stable carbonium ions. Thus the direction of rearrangement is usually primary ⟶ secondary ⟶ tertiary. Neopentyl (Me_3CCH_2), neophyl ($PhCMe_2CH_2$), and norbornyl (e.g., **3**) type systems are especially prone to carbonium-ion rearrangement reactions.



3

The Actual Nature of the Migration. Most anionotropic 1,2-shifts are intramolecular: W does not become free but always remains connected in some way to the substrate. Aside from the evidence from crossover experiments, the strongest evidence is that, when the group W is optically active, the configuration is *retained* in the product. For example (+)-PhCHMeCOOH was converted to (−)-$PhCHMeNH_2$ by the Curtius (**8-16**), Hofmann (**8-15**), Lossen (**8-17**), and Schmidt (**8-18**) reactions.[7] In these reactions the extent of retention varied from 95.8 to 99.6%. Retention of configuration in the migrating group has been shown many times since. Another experiment demonstrating retention was the easy conversion of **4** to **5.**[8]

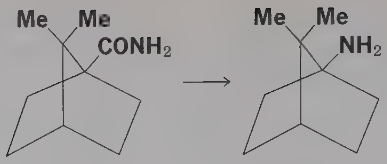
[4] Hauser and Kantor, *J. Am. Chem. Soc.* **72,** 4284 (1950).

[5] Brower, *J. Am. Chem. Soc.* **83,** 4370 (1961).

[6] Dostrovsky and Hughes, *J. Chem. Soc.* **1946,** 166.

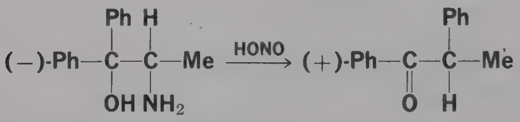
[7] Arcus and Kenyon, *J. Chem. Soc.* **1939,** 916; Kenyon and Young, *J. Chem. Soc.* **1941,** 263; Campbell and Kenyon, *J. Chem. Soc.* **1946,** 25.

[8] Bartlett and Knox, *J. Am. Chem. Soc.* **61,** 3184 (1939).



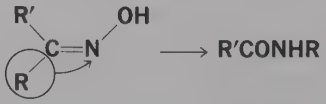
4 5

Neither inversion nor racemization could take place at a bridgehead. There is much other evidence that retention of configuration usually occurs in W, and inversion never.[9] However, this is not the state of affairs at A and B. In many reactions, of course, the structure of W—A—B is such that the product has only one steric possibility at A or B or both, and in most of these cases nothing can be learned. But in cases where the steric nature of A or B can be investigated, the results are mixed. It has been shown that either inversion or racemization can occur at A or B. Thus the following conversion proceeded with inversion at B:[10]



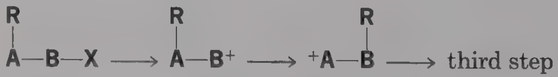
$$(-)\text{-Ph}-\underset{\text{OH}}{\overset{\text{Ph}}{\text{C}}}-\underset{\text{NH}_2}{\overset{\text{H}}{\text{C}}}-\text{Me} \xrightarrow{\text{HONO}} (+)\text{-Ph}-\underset{\text{O}}{\overset{}{\text{C}}}-\underset{\text{H}}{\overset{\text{Ph}}{\text{C}}}-\text{Me} \qquad \text{(reaction 8-2)}$$

and inversion at A has been shown in other cases.[11] However, in many other cases, racemization occurs at A or B or both.[12] It is not always necessary for the product to have two steric possibilities in order to investigate the stereochemistry at A or B. Thus, in most Beckmann rearrangements (reaction **8-19**), only the group trans (usually called *anti*) to the hydroxyl group migrates:



showing inversion at B, though no optical activity is involved.

This information tells us about the degree of concertedness of the three steps of the rearrangement. First we shall look at the migration terminus B. If racemization is found at B, then it is probable that the first step takes place before the second, and that a carbonium-ion carbon (or other sextet atom) is present at B:



$$\overset{\text{R}}{\text{A}}-\text{B}-\text{X} \longrightarrow \overset{\text{R}}{\text{A}}-\text{B}^{+} \longrightarrow {}^{+}\text{A}-\overset{\text{R}}{\text{B}} \longrightarrow \text{third step}$$

---

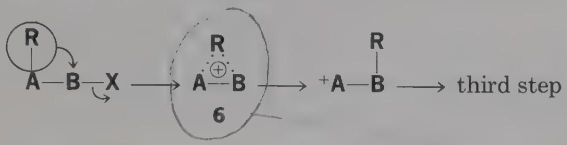
[9] See Cram, in Newman, "Steric Effects in Organic Chemistry," pp. 251–254, John Wiley & Sons, Inc., New York, 1956; Ref. 2, pp. 597–604.

[10] Bernstein and Whitmore, *J. Am. Chem. Soc.* **61,** 1324 (1939).

[11] For example, see Meerwein and van Emster, *Ber.* **53,** 1815 (1920), **55,** 2500 (1922); Meerwein and Gérard, *Ann.* **435,** 174 (1923).

[12] For example, see Winstein and Morse, *J. Am. Chem. Soc.* **74,** 1133 (1952).

With respect to B this is an S_N1-type process. If inversion occurs at B, then it is likely that the first two steps are concerted, that a carbonium ion is *not* an intermediate, and that the process is S_N2-like:

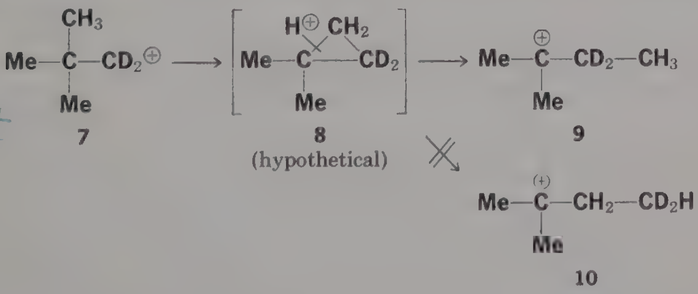


In this case participation by R is assisting removal of X in the same way that neighboring groups do (p. 263). Indeed, R *is* a neighboring group here, and the only difference is that, in the case of the neighboring-group mechanism of nucleophilic substitution, R never becomes detached from A, while in a rearrangement the bond between R and A is broken. **6** may be a true intermediate or only a transition state, depending on what migrates. However, inversion of configuration at B does not *necessarily* indicate an S_N2-like process. The intermediate ion may be configurationally stable in the form generated.

Cram[9] presents a full discussion of these points, but we may summarize a few conclusions here:

1. The S_N1-type process occurs mostly when B is a tertiary atom or has one aryl group and at least one other alkyl or aryl group. In other cases, the S_N2-type process is more likely.

2. When R is aryl or vinyl, then **6** is probably an intermediate (see p. 130 for resonance stabilization of the aryl intermediate), but when R is alkyl, **6** is generally a transition state. This was shown by experiments involving labeling. Rearrangement of the neopentyl cation labeled with deuteriums in the 1-position (**7**) gave only *tert*-amyl products with the label in the 3-position (derived from **9**), though if **8** were an intermediate, the cyclopropane ring could just as well cleave the other way to give *tert*-amyl derivatives labeled in the 4-position (derived from **10**).[13] This is in spite of the fact that cyclopropane derivatives can be isolated from neopentyl cations.[14] The cyclopropane compounds must be formed in an irreversible process (at least under the conditions of formation). Another experiment which led to the



ument

---

[13] Skell, Starer, and Krapcho, *J. Am. Chem. Soc.* **82**, 5257 (1960).

[14] Skell and Starer, *J. Am. Chem. Soc.* **82**, 2971 (1960); Silver, *J. Am. Chem. Soc.* **82**, 2971 (1960).

same conclusion was the generation, in several ways, of $Me_3C^{13}CH_2^+$. In this case the only *tert*-amyl products isolated were labeled in C-3, that is, $Me_2\overset{\oplus}{C}—{}^{13}CH_2CH_3$ derivatives; no derivatives of $Me_2\overset{\oplus}{C}—CH_2{}^{13}CH_3$ were found.[15] However, when cations were generated from labeled propyl systems ($CH_3CD_2CH_2^+$, $CH_3CH_2CD_2^+$, $CH_3CH_2{}^{14}CH_2^+$), isotopic distribution in the products indicated that a small amount (about 5%) of the product had to be formed from protonated cyclopropane intermediates, e.g.,[16]

$$CH_3CH_2CD_2NH_2 \xrightarrow{HONO} \sim 1\%\ C_2H_4D—CHD—OH$$

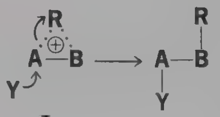
$$CH_3CD_2CH_2NH_2 \xrightarrow{HONO} \sim 1\%\ C_2H_4D—CHD—OH$$

$$CH_3CH_2{}^{14}CH_2NH_2 \xrightarrow{HONO} \sim 2\%\ {}^{14}CH_3CH_2CH_2OH + \sim 2\%\ CH_3{}^{14}CH_2CH_2OH$$

In addition, **6** may be an intermediate in systems where nonclassical carbonium ions (p. 130) are possible.

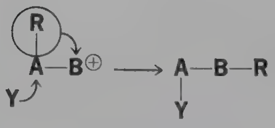
3. There has been much discussion of H as migrating group. There is no conclusive evidence for the viewpoint that **6** in this case is a true intermediate or that it is not, though both positions have been argued.

The stereochemistry at the migration origin A is less often involved, since in most cases it does not end up as a tetrahedral atom, but when there is inversion here, there is an S_N2-type process at the beginning of the migration. This may or may not be accompanied by an S_N2 process at the migration terminus B:



6

inversion at A and B



inversion at A only

In some cases it has been found that, when H is the migrating species, the configuration at A may be *retained.*[17]

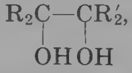
---

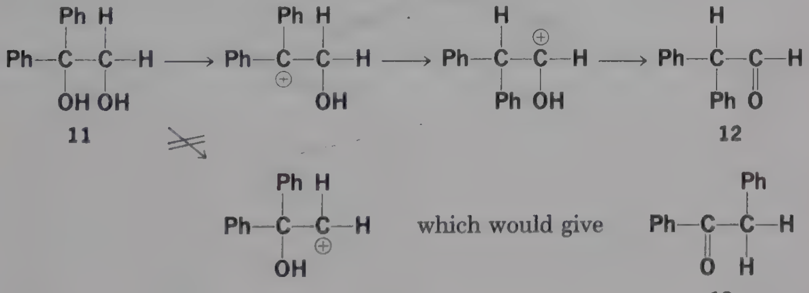
[15] Karabatsos and Graham, *J. Am. Chem. Soc.* **82**, 5250 (1960); Karabatsos, Orzech, and Meyerson, *J. Am. Chem. Soc.* **86**, 1994 (1964).

[16] Lee, Kruger, and Wong, *J. Am. Chem. Soc.* **87**, 3985 (1965); Lee and Kruger, *J. Am. Chem. Soc.* **87**, 3986 (1965), *Tetrahedron* **23**, 2539 (1967); Karabatsos, Orzech, and Meyerson, *J. Am. Chem. Soc.* **87**, 4394 (1965).

[17] Winstein and Holness, *J. Am. Chem. Soc.* **77**, 5562 (1955); Cram and Tadanier, *J. Am. Chem. Soc.* **81**, 2737 (1959).

Migratory Aptitudes.[18] In many reactions there is no question about which group migrates. For example, in the Hofmann, Curtius, and similar reactions there is only one possible migrating group in each molecule, and one can measure migratory aptitudes only by comparing the relative rearrangement rates of different compounds. In other instances there are two or more potential migrating groups, but which migrates is settled by the geometry of the molecule. The Beckmann rearrangement (reaction **8-19**) provides an example. As we have seen, only the group trans to the OH migrates. In compounds whose geometry is not restricted in this manner, there still may be eclipsing effects (see p. 733), so that the choice of migrating group is largely determined by which group is in the right place in the most stable conformation of the molecule.[19] However, in some reactions, especially the Wagner-Meerwein (**8-1**) and the pinacol (**8-2**) rearrangements, the molecule may contain several groups, which, geometrically at least, have approximately equal chances of migrating, and these reactions permit a direct study of relative migratory aptitudes. In the pinacol rearrangement there is the additional question of which OH group leaves and which does not, since a group can migrate only if the OH group on *the other* carbon is lost.

We shall deal with the second question first. To study this question, the best type of substrate to use is one of the form  $R_2\underset{OH}{C}—\underset{OH}{C}R'_2$, since the only thing that determines migratory aptitude is which OH group comes off. Once the OH group is gone, the migrating group is determined. As might be expected, the OH which leaves is the one whose loss gives rise to the more stable carbonium ion. Thus 1,1-diphenylethanediol (**11**) gives diphenylacetaldehyde (**12**) and not phenylacetophenone (**13**).



11 **12** **14** **13**

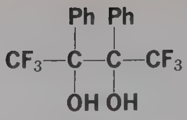
Obviously it does not matter in this case whether phenyl has a greater inherent migratory aptitude than hydrogen or not. Only the hydrogen can migrate because **14** is not formed. As we have already seen, carbonium-ion stability is enhanced by groups in the order aryl > alkyl > hydrogen. Where inductive effects act to decrease carbonium-ion stability greatly, rearrangement may not take place at all. Thus **15** is remarkably resistant to the pinacol rearrangement.[20]

---

[18] For a discussion, see Ref. 2, pp. 573–597.

[19] For a discussion, see Cram, Ref. 9, pp. 270–276.

[20] Mosher and Heindel, *J. Am. Chem. Soc.* **85**, 1548 (1963).

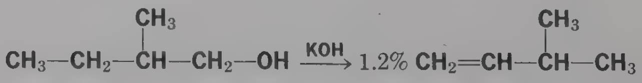


$$CF_3-\underset{OH}{\overset{Ph}{C}}-\underset{OH}{\overset{Ph}{C}}-CF_3$$

15

In order to answer the question about inherent migratory aptitudes, the obvious type of substrate to use (in the pinacol rearrangement) is $\underset{OH}{RR'C}-\underset{OH}{CRR'}$, since the same carbonium ion is formed no matter which OH leaves, and there is thus a direct comparison of the migrating tendencies of R and R′. However, the question does not have a clear-cut answer. More often than not, the migration order is hydrogen > aryl > alkyl, but many exceptions are known. Mixtures are often found, and the isomer which predominates often depends on conditions. Among aryl migrating groups, electron-donating substituents in the para and meta positions increase the migratory aptitudes, while the same substituents in the ortho positions decrease them. Electron-withdrawing groups decrease migrating ability in all positions. The following are a few of the relative migratory aptitudes determined for aryl groups by Bachmann and Ferguson:[21] *p*-anisyl, 500; *p*-tolyl, 15.7; *m*-tolyl, 1.95; phenyl, 1.00; *p*-chlorophenyl, 0.7; *o*-anisyl, 0.3. For the *o*-anisyl group, the poor migrating ability probably has a steric cause, while for the others there is a fair correlation with activation or deactivation of electrophilic aromatic substitution, which is what the process is, with respect to the benzene ring.

Longer Anionotropic Rearrangements. Rearrangements in which a group carries an electron pair from A to C in W—A—B—C or over longer distances are rare[22] (not counting allylic shifts, see p. 270). Indeed, whether 1,3- (and longer) rearrangements occur at all in acyclic systems is still a matter of controversy. Although claims have been made that alkyl groups can migrate in this way,[23] most discussion has concerned 1,3-hydride shifts.[24] Many *apparent* 1,3-hydride shifts have been found, but the difficulty is that it is possible for an apparent 1,3-hydride shift to be actually caused by two successive 1,2-shifts. Many attempts have been made to show that apparent 1,3-shifts actually are 1,3-shifts. For example, the reaction of 2-methyl-1-butanol with KOH and bromoform gave a mixture of olefins, nearly all of which could have arisen from simple elimination or 1,2-shifts of hydride or alkyl. However, 1.2% of the product was 3-methyl-1-butene (**16**):[25]



$$CH_3-CH_2-\overset{CH_3}{CH}-CH_2-OH \xrightarrow{KOH} 1.2\%\ CH_2{=}CH-\overset{CH_3}{CH}-CH_3$$

16

---

[21] Bachmann and Ferguson, *J. Am. Chem. Soc.* **56**, 2081 (1934).

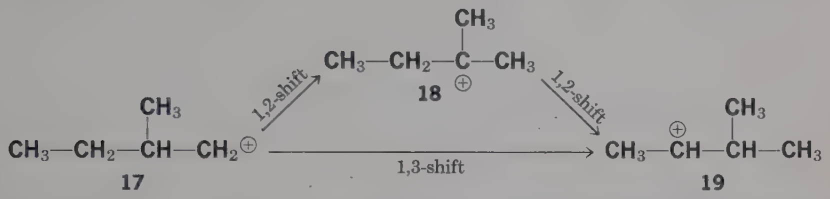
[22] Saunders and Carges, *J. Am. Chem. Soc.* **82**, 3582 (1960).

[23] For example, see Carlin and Moores, *J. Am. Chem. Soc.* **81**, 1259 (1959).

[24] For a review, see Reutov, *Pure Appl. Chem.* **7**, 203–227 (1963).

[25] Skell and Maxwell, *J. Am. Chem. Soc.* **84**, 3963 (1962). See also Skell and Starer, *J. Am. Chem. Soc.* **84**, 3962 (1962).

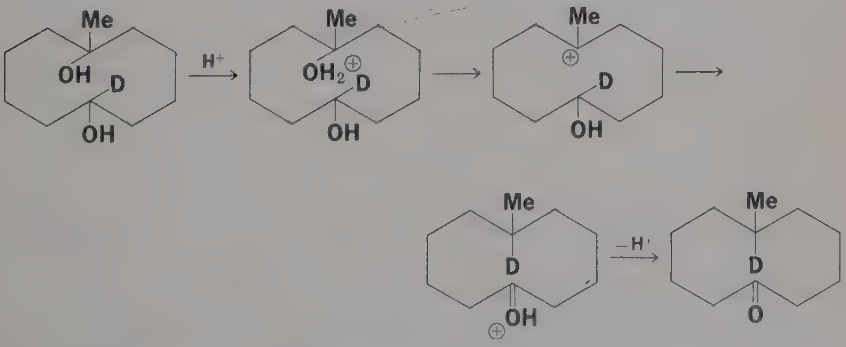
Hypothetically, **16** could have arisen from a 1,3-shift or from two successive 1,2-shifts:



However, the same reaction applied to 2-methyl-2-butanol gave no **16**, which demonstrated that **19** was not formed from **18**. The conclusion was thus made that **19** was formed directly from **17** by a 1,3-hydride shift. However, it is also possible that **16** was formed not by a 1,3-hydride shift, but through a protonated cyclopropane (see p. 786). Labeling experiments involving deuterium, tritium, and ^{14}C have been used in attempts to distinguish between 1,3-shifts and successive 1,2-shifts, but contradictory results have been reported.[26]

Even longer hydride shifts have been reported. $CH_3(CH_2)_5CH{=}CH_2$, when treated with peroxytrifluoroacetic acid (reaction **5-28**, p. 616), gave mostly the unrearranged product 1,2-octanediol. But small amounts of the 1,3-, 1,4-, 1,5-, 1,6-, and 1,7-diols were also obtained.[27] These products could have arisen from successive 1,2-shifts, but the ratio of the yields obtained makes it unlikely.

Although anionotropic rearrangements over distances greater than 1,2 are rare (or perhaps nonexistent) when the migrating atom or group must move along a chain, this is not so for a shift across a ring of eight to eleven members. Many such transannular rearrangements are known.[28] Several examples are given on page 121. We may look at the mechanism of one of these:[29]



---

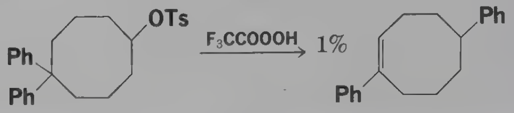
[26] Ref. 24; Ref. 16; Reutov and Shatkina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963**, 180; Karabatsos and Orzech, *J. Am. Chem. Soc.* **84**, 2838 (1962).

[27] Cope, Fleckenstein, Moon, and Petree, *J. Am. Chem. Soc.* **85**, 3752 (1963).

[28] For reviews, see Prelog and Traynham, in Ref. 1, vol. 1, pp. 593–615; and Cope, Martin, and McKervey, *Quart. Rev. (London)* **20**, 119–152 (1966). For many references, see Blomquist and Buck, *J. Am. Chem. Soc.* **81**, 672 (1951).

[29] Prelog and Küng, *Helv. Chim. Acta* **39**, 1394 (1956).

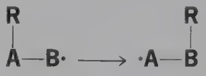
It is noteworthy that the *methyl* group does not migrate in this system. It is generally true that alkyl groups do not undergo transannular migration. Most of the time it is hydride which undergoes this type of migration, although a small amount of phenyl migration has also been shown:[30]



Free-radical Rearrangements.[31] 1,2-Free-radical rearrangements are much less common than the anionotropic type previously considered since free radicals are much less prone to rearrange than are carbonium ions. Where they do occur, the general pattern is similar. There must first be generation of a free radical, then the actual migration, in which the migrating group moves with one electron:

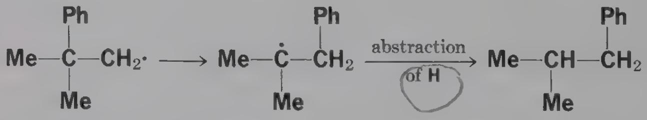
neration

ctual
migration



$$\mathrm{\underset{\displaystyle A}{\overset{R}{|}}{-}B\cdot \longrightarrow \cdot A{-}\underset{\displaystyle B}{\overset{R}{|}}}$$

Finally, the new free radical must stabilize itself by a further reaction. The order of radical stability would lead us to predict that here too, as with carbonium-ion rearrangements, any migrations should be in the order primary ⟶ secondary ⟶ tertiary, and that the logical place to look for them should be in neopentyl and neophyl systems. The most common way of generating free radicals for the purpose of detection of rearrangements is by decarbonylation of aldehydes (reaction **4-27,** p. 560). In this manner it was found that neophyl radicals *do* undergo rearrangement. Thus, $PhCMe_2CH_2CHO$, treated with di-*tert*-butyl peroxide, gave about equal amounts of the normal product $PhCMe_2CH_3$ and the product arising from migration of phenyl:[32]



$$\mathrm{Me{-}\underset{Me}{\overset{Ph}{C}}{-}CH_2\cdot \longrightarrow Me{-}\underset{Me}{\dot{C}}{-}\overset{Ph}{CH_2} \xrightarrow[\text{of H}]{\text{abstraction}} Me{-}\underset{Me}{CH}{-}\overset{Ph}{CH_2}}$$

Other cases of aryl free-radical migration have also been found.[33]

It is noteworthy that the extent of migration is much less than with the corresponding carbonium ions: thus in the example given there was only about 50% migration, whereas the carbonium ion would give much more. Also noteworthy is that there was no migration of the methyl group. In general it may be said that free-radical migration of alkyl groups does not occur at ordinary temperatures. Many attempts have been made to detect such migration on the traditional neopentyl and bornyl types of substrates. However, alkyl migration is not observed,[34] even in substrates where the corresponding carbonium ions undergo facile rearrangement.[35] Another type of migration which is very common for carbonium ions, but which is not observed for free radicals, is 1,2-migration of hydrogen. We confine ourselves to a few examples of the lack of migration of alkyl groups and hydrogen:

---

[30] Cope, Burton, and Caspar, *J. Am. Chem. Soc.* **84,** 4855 (1962).

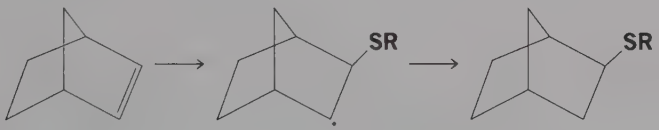
[31] For reviews, see Walling, in Ref. 1, vol. 1, pp. 407–455; Fish, *Quart. Rev.* (*London*) **18,** 243–269 (1964); Freidlina, Kost, and Khorlina, *Russ. Chem. Rev.* **31,** 1–18 (1962), and Freidlina, *Advan. Free Radical Chem.* **1,** 211–278 (1965). For a review of photochemical rearrangements (not considered here), see Mayo and Reid, *Quart. Rev.* (*London*) **15,** 393–417 (1961).

[32] Winstein and Seubold, *J. Am. Chem. Soc.* **69,** 2916 (1947); Seubold, *J. Am. Chem. Soc.* **75,** 2532 (1953).

[33] For example, see Curtin and Hurwitz, *J. Am. Chem. Soc.* **74,** 5381 (1952); Wilt and Philip, *J. Org. Chem.* **24,** 441 (1959), **25,** 891 (1960); Pines and Pillai, *J. Am. Chem. Soc.* **82,** 2921 (1960); Pines and Goetschel, *J. Am. Chem. Soc.* **87,** 4207 (1965); Mulcahy, Tucker, Williams, and Wilmshurst, *Chem. Commun.* **1965,** 609 (in the latter case, from oxygen to carbon).

1. 3,3-Dimethylpentanal ($EtCMe_2CH_2CHO$) gave no rearranged products upon decarbonylation.[36]

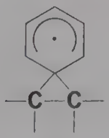
2. Addition of RSH to norbornene (**20**) gave only *exo*-norbornyl sulfides, though **21** is an intermediate, and the corresponding carbonium ion cannot be formed without rearrangement.[37]



20 **21**

3. It was shown[38] that no rearrangement of isobutyl radical to *tert*-butyl radical (which would involve the formation of a more stable radical by a hydrogen shift) took place during the chlorination of isobutane.

The fact that aryl groups migrate, but generally alkyl groups and hydrogen do not, leads to the proposition that the activation energy of the former process is lowered by the formation of a bridged intermediate (**22**), analogous



22

to the arylonium ions postulated on page 130. There has been much controversy on this point, and kinetic and steric evidence has been presented against it.[39] It is probable that, even if these intermediates exist, they are formed *after* formation of the initial free radical; that is, they do not lend anchimeric assistance to this formation: decomposition of Ph_3CCH_2CHO gave about 4% $Ph_3CCH_2CH_2CPh_3$.[40] This must have been formed by dimerization of $Ph_3CCH_2\cdot$. But if migration of phenyl were helping the CO to leave, then such radicals would not be present.

---

[34] Formal migration of alkyl has been observed, but by an elimination-addition mechanism: Berson, Olsen, and Walia, *J. Am. Chem. Soc.* **84**, 3337 (1962).

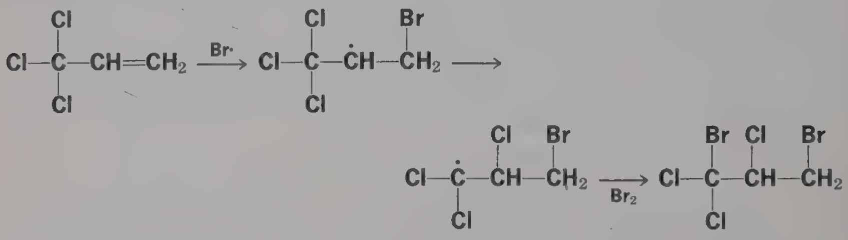
[35] For a summary of unsuccessful attempts, see Slaugh, Magoon, and Guinn, *J. Org. Chem.* **28**, 2643 (1963).

[36] Seubold, *J. Am. Chem. Soc.* **76**, 3732 (1954).

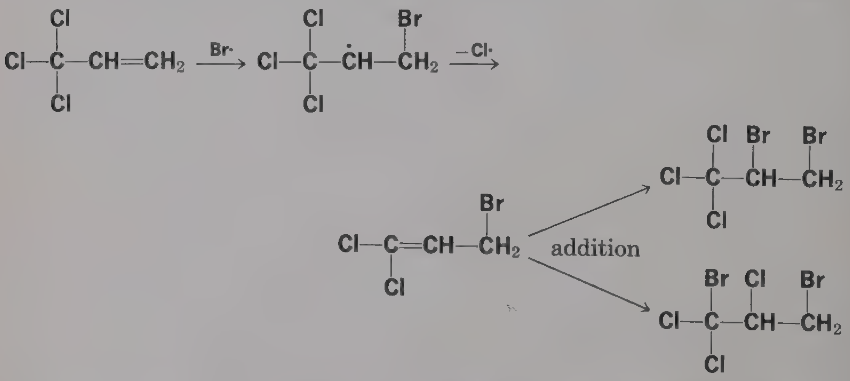
[37] Cristol and Brindell, *J. Am. Chem. Soc.* **76**, 5699 (1954).

[38] Brown and Russell, *J. Am. Chem. Soc.* **74**, 3995 (1952).

Besides aryl groups, vinyl groups also migrate.[41] In addition, migration has been suggested for chloro and bromo groups, on the basis of experiments such as the following: in the reaction of $Cl_3CCH{=}CH_2$ with bromine under the influence of peroxides, the products were 47% $Cl_3CCHBrCH_2Br$ (the normal addition product) and 53% $BrCCl_2CHClCH_2Br$, which, it is proposed, arose by rearrangement:



In this particular case the driving force for the rearrangement would be the particular stability of dichloroalkyl free radicals. Nesmeyanov, Freidlina, and coworkers have exhaustively studied reactions of this sort.[42] However, it has been pointed out that these results might also have been caused, at least in part, by an allylic shift followed by addition:[43]



In summary then, 1,2 free-radical migrations are less prevalent than the analogous carbonium-ion processes and are important only for aryl, vinyl, and perhaps halogen migrating groups. The direction of migration is normally toward the more stable radical, but "wrong-way" rearrangements are also known.[44]

---

[39] Martin, *J. Am. Chem. Soc.* **84**, 1986 (1962); Rüchardt and Hecht, *Tetrahedron Letters* **1962**, 957, *Chem. Ber.* **98**, 2460, 2471 (1965); Rüchardt and Trautwein, *Chem. Ber.* **98**, 2478 (1965).

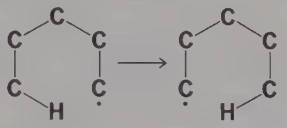
[40] Denney, Ellsworth, and Denney, *J. Am. Chem. Soc.* **86**, 1116 (1964).

[41] For example, see Slaugh, Mullineaux, and Raley, *J. Am. Chem. Soc.* **85**, 3180 (1963); Slaugh, *J. Am. Chem. Soc.* **87**, 1522 (1965).

[42] For reviews, see Nesmeyanov, Freidlina, Kost, and Khorlina, *Tetrahedron* **16**, 94–105 (1961); Freidlina, Kost, and Khorlina, Ref. 31, pp. 6–11.

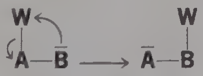
[43] Haag and Heiba, *Tetrahedron Letters* **1965**, 3683.

Despite the fact that hydrogen atoms do not migrate 1,2, longer free-radical migrations of hydrogen are known. The most common are 1,5-shifts, but 1,3-, 1,4-, 1,6-, and longer shifts have been found. In fact it has been shown that, in the gas phase, the reason that 1,2-hydrogen shifts are not observed is not that they do not occur, but that they are swamped by energetically more favorable 1,4- and 1,5-shifts.[45] These long shifts may be regarded as internal abstractions of hydrogen (for reactions involving them, see **4-7** and **8-32**):



Transannular shifts of hydrogen atoms have also been observed.[46] A few shifts longer than 1,2 have been noted for aryl, but not for alkyl or halogen groups.

Cationotropic Rearrangements.[47] Rearrangements in which a group migrates without its electrons are much rarer than the two kinds previously considered, but the general principles are the same. There is first created a carbanion (or other negative ion), and the actual rearrangement step involves migration of a group without its electrons:



The product of the rearrangement may be stable or may react further, depending on its nature (see also p. 798).

REACTIONS

The reactions in this chapter are classified into two main groups. 1,2-Shifts are considered first. Within this group, reactions are classified according to (1) the identity of the substrate atoms A and B and (2) the nature of the migrating group W. In the second group are the non-1,2-shifts.

Reactions in which the migration terminus is on an aromatic ring have been treated under aromatic substitution. These are reactions **1-31** to **1-37**, **1-41**, **3-26** to **3-29**, and, partially, **1-38**, **1-44**, and **1-45**. Double-bond shifts have also been treated in other chapters, though they may be considered rearrangements (p. 270, p. 449, and reaction **2-2**). Two other reactions which may be regarded as rearrangements are the Willgerodt reaction (**9-64,** p. 910) and the decomposition of tertiary hypochlorites (**4-28,** p. 560).

---

[44] Slaugh, *J. Am. Chem. Soc.* **81**, 2262 (1959); Slaugh and Raley, *J. Am. Chem. Soc.* **82**, 1259 (1960); Bonner and Mango, *J. Org. Chem.* **29**, 29 (1964).

[45] Fish, *Quart. Rev. (London)* **18**, 243–269 (1964), 247.

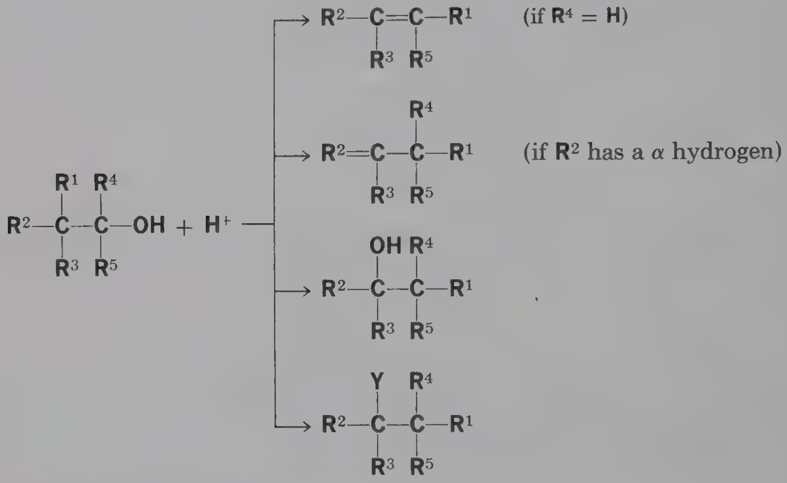
[46] Heusler and Kalvoda, *Tetrahedron Letters* **1963**, 1001; Cope, Bly, Martin, and Petterson, *J. Am. Chem. Soc.* **87**, 3111 (1965); Fisch and Ourisson, *Chem. Commun.* **1965**, 407.

[47] For a review, see Cram, "Fundamentals of Carbanion Chemistry," pp. 223–243, Academic Press Inc., New York, 1965.

1,2-Rearrangements

A. Carbon-to-carbon migrations of R, H, and Ar

8-1 Wagner-Meerwein and related reactions



R = alkyl, aryl, or hydrogen

When alcohols are treated with acids, simple substitution (e.g., reaction **0-64,** p. 343) or elimination (reaction **7-1,** p. 753) usually accounts for most or all of the products. But in many cases, especially where two or three alkyl or aryl groups are on the β-carbon, some or all of the product is rearranged. These rearrangements are called *Wagner-Meerwein rearrangements.*[48] As pointed out previously (p. 782), the carbonium ion which is a direct product of the rearrangement must stabilize itself, and most often it does this by the loss of a hydrogen β to it, so that the rearrangement product is usually an olefin. The proton lost may be R^4 (if this is a hydrogen) or an α proton from R^2 (if it has one). If there is a choice of protons, Zaitsev's rule (p. 739) governs the direction, as we might expect. Sometimes a different positive group is lost instead of a proton.[49] Less often, the new carbonium ion stabilizes itself by combining with a nucleophile instead of losing a proton. The nucleophile may be the water which is the original leaving group, so that the product is a rearranged alcohol, or it may be some other species present, which we have called Y. Rearrangement is usually predominant in neopentyl and neophyl types of substrates, and with these types normal nucleophilic substitution is difficult (normal elimination is, of course, impossible): under S_N2 conditions substitution is extremely slow, and under S_N1 conditions carbonium ions are formed which rapidly rearrange.

---

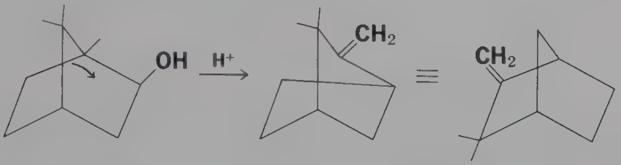
[48] For a review, see Pocker, in Ref. 1, vol. 1, pp. 6–15.

[49] For example, see Grob, Hoegerle, and Ohta, *Helv. Chim. Acta* **45**, 1823 (1962).

However, free-radical substitution, unaccompanied by rearrangement, may be carried out on neopentyl systems, though, as we have seen (p. 790), neophyl systems undergo rearrangement as well as substitution.

Wagner-Meerwein rearrangements were first discovered in the bicyclic terpenes, and most of the early development of this reaction was with these compounds.[50] For this reason they are often illustrated with an example from the terpenes, e.g.,

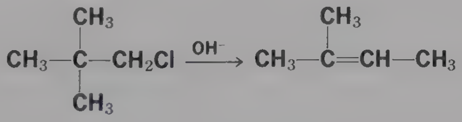
Example *a*[51]



Isoborneol Camphene

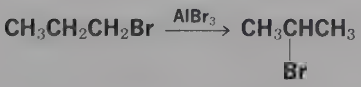
However, they may be illustrated in simpler systems:

Example *b*



$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_2Cl \xrightarrow{OH^-} CH_3-\overset{\displaystyle CH_3}{\overset{|}{C}}=CH-CH_3$$

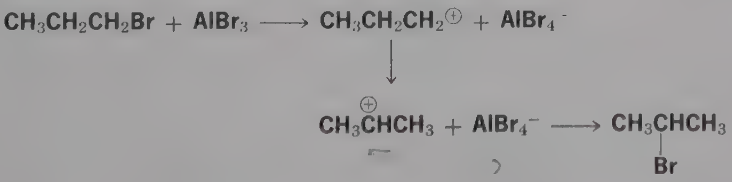
Example *c*



$$CH_3CH_2CH_2Br \xrightarrow{AlBr_3} CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_3$$

These examples illustrate the following points:

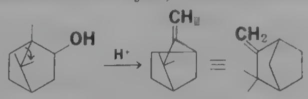
1. Hydride ion may migrate. In example *c*, it was hydride that shifted, and not bromide:



$$\begin{array}{lll} CH_3CH_2CH_2Br + AlBr_3 \longrightarrow & CH_3CH_2CH_2^{\oplus} + AlBr_4^- & \\ & \downarrow & \\ & CH_3\overset{\oplus}{C}HCH_3 + AlBr_4^- \longrightarrow & CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 \end{array}$$

[50] For a review of rearrangements of bicyclic systems, see Berson, in Ref. 1, pp. 111–231. For reviews of the Wagner-Meerwein rearrangement applied to natural products, see Ref. 1 as follows: terpenes, King and Mayo, pp. 813–840; alkaloids, Warnhoff, pp. 842–879; steroids, Wendler, pp. 1020–1028. A review concerning pinanes is by Banthorpe and Whittaker, *Quart. Rev. (London)* **20**, 373–387 (1966).

[51] Before the advent of conformational analysis, this reaction was written



Isoborneol Camphene

2. The leaving group does not have to be H_2O, but it may be any departing species whose loss creates a carbonium ion, including N_2 from aliphatic diazonium ions (see the section on leaving groups in nucleophilic substitution, p. 290). Also rearrangement may follow when the carbonium ion is created by addition of a proton or other positive species to a double bond. Even alkanes give rearrangements when heated with Lewis acids, provided there is some species present initially to form a carbonium ion from the alkane.

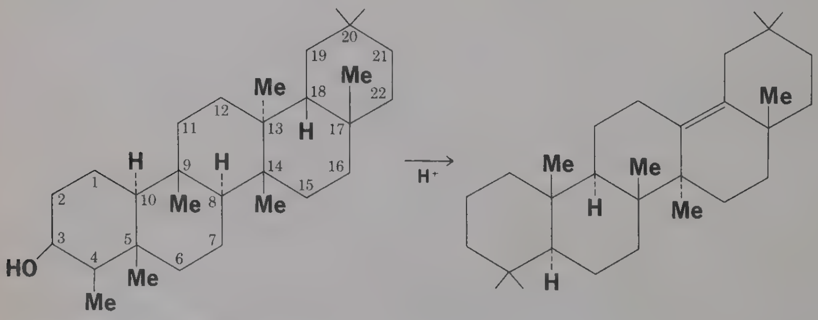
3. Example *c* illustrates that the last step may be substitution instead of elimination.

4. Example *b* illustrates that the new double bond is formed in accord with Zaitsev's rule.

The direction of rearrangement is usually in the direction of the most stable carbonium ion (or free radical), which is tertiary > secondary > primary, but rearrangements in the other direction have also been found, and often the product is a mixture corresponding to an equilibrium mixture of the possible carbonium ions. The favored direction may be counter to carbonium-ion stability if the new carbonium ion can stabilize itself more easily than the original one.

The term "Wagner-Meerwein rearrangement" is not precise. Some use it to refer to all of the rearrangements in this section and in **8-2.** Others use it only when an alcohol is converted to a rearranged olefin. Terpene chemists call the migration of a methyl group the *Nametkin rearrangement.* The term *retropinacol rearrangement* is often applied to some or all of these. Fortunately, this disparity in nomenclature does not seem to cause much confusion.

Sometimes several of these rearrangements occur in one molecule either simultaneously or in rapid succession. A spectacular example is found in the triterpene series. Friedelin is a triterpenoid ketone found in cork. Reduction gives 3β-friedelanol (**23**). When this compound is treated with acid, 13(18)-oleanene (**24**) is formed.[52] In this case *seven* 1,2-shifts take place. Upon removal of H_2O from position 3 to leave a positive charge, the following



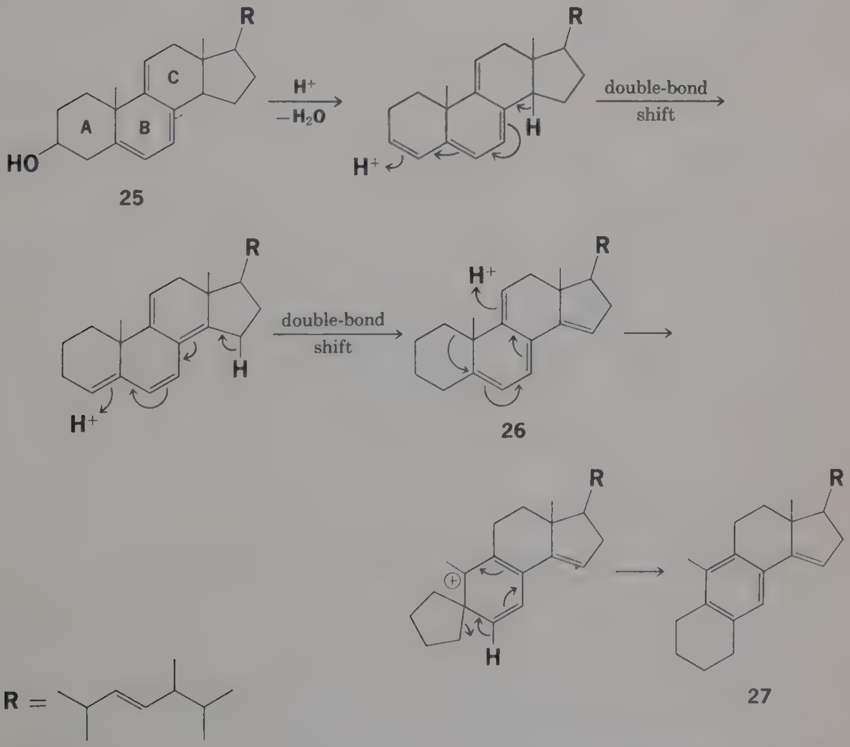
23 **24**

---

[52] Corey and Ursprung, *J. Am. Chem. Soc.* **78**, 5041 (1956).

shifts occur: hydride from 4 to 3; methyl from 5 to 4; hydride from 10 to 5; methyl from 9 to 10; hydride from 8 to 9; methyl from 14 to 8; and methyl from 13 to 14. This leaves a positive charge at position 13, which is stabilized by loss of the proton at the 18 position to give the 13(18)-ene. Until the elimination, each time a positive charge is formed, a migration of a hydride or a methyl moves in to fill it, leaving another positive charge, which must be filled in its turn. All of these shifts are stereospecific, the group always migrating on the side of the ring system on which it is located; that is, a group above the "plane" of the ring system (indicated by a solid line in **23**) moves above the plane, and a group below the plane (dotted line) moves below it. It is probable that the seven shifts are not all concerted, though some of them may be, for intermediate products can be isolated. As an illustration of point 2 (p. 796), it may be mentioned that friedelene, derived from dehydration of **23**, also gives **24** upon treatment with acid.[53]

An interesting Wagner-Meerwein rearrangement is found in the steroid series. The A-B-C rings of a steroid are changed from an angular (phenanthrene-like) arrangement to a linear (anthracene-like) one. This is called the *anthrasteroid rearrangement,* and it may be illustrated for dehydroergosterol (**25**):

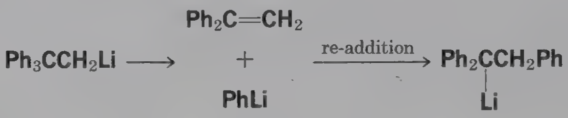


---

[53] Dutler, Jeger, and Ruzicka, *Helv. Chim. Acta* **38**, 1268 (1955); Brownlie, Spring, Stevenson, and Strachan, *J. Chem. Soc.* **1956**, 2419.

The product is anthraergostapentaene (**27**). The intermediate **26** has been isolated.

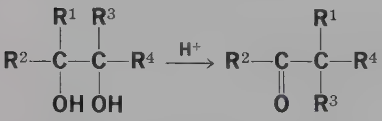
As has already been indicated, the mechanism of the Wagner-Meerwein rearrangement is usually anionotropic. Free-radical rearrangements are also known (see the mechanism section of this chapter), though virtually only with aryl migration. However, carbanion mechanisms (cationotropic) have also been found.[54] Thus Ph_3CCH_2Cl treated with sodium gave Ph_2CHCH_2Ph along with unrearranged products.[55] The intermediate is $Ph_3C\bar{C}H_2^{\ominus}$, and the phenyl moves without its electron pair. Rearrangements were also obtained with potassium, but less with lithium, and not at all with magnesium, indicating that a relatively free carbanion is required. There is evidence that in at least one case an elimination-addition mechanism is responsible for what is an apparent cationotropic rearrangement:[56]



$$Ph_3CCH_2Li \longrightarrow Ph_2C{=}CH_2 + PhLi \xrightarrow{\text{re-addition}} \underset{\displaystyle Li}{Ph_2\overset{|}{C}}CH_2Ph$$

OS **45,** 12.

8-2 The pinacol rearrangement



$$R^2{-}\overset{\displaystyle R^1}{\underset{\displaystyle OH}{C}}{-}\overset{\displaystyle R^3}{\underset{\displaystyle OH}{C}}{-}R^4 \xrightarrow{H^+} R^2{-}\underset{\displaystyle O}{\overset{\|}{C}}{-}\overset{\displaystyle R^1}{\underset{\displaystyle R^3}{C}}{-}R^4$$

R = alkyl, aryl, or hydrogen

When *vic*-diols are treated with acids, they may be rearranged to give aldehydes or ketones, though elimination without rearrangement can also be accomplished. This reaction is called the *pinacol,* or the *pinacol-pinacolone rearrangement,* the reaction getting its name from the typical compound pinacol $Me_2COHCOHMe_2$, which is rearranged to pinacolone Me_3CCOCH_3.[57] The reaction has been accomplished many times, with alkyl, aryl, and hydrogen as migrating groups. In most cases each carbon has at least one alkyl or aryl group, and the reaction is most often carried out with tri- and tetrasubstituted glycols.

The mechanism involves a simple Whitmore 1,2-shift, in which the driving force is stabilization of the new carbonium ion by elimination of a proton from the OH:

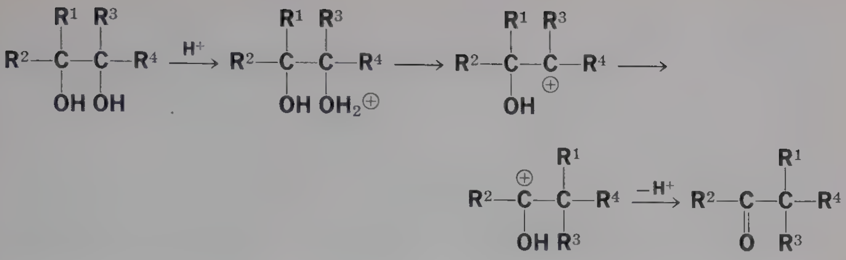
---

[54] For a review, see Cram, "Fundamentals of Carbanion Chemistry," pp. 233–238, Academic Press Inc., New York, 1965.

[55] Grovenstein, *J. Am. Chem. Soc.* **79,** 4985 (1957); Zimmerman and Smentowski, *J. Am. Chem. Soc.* **79,** 5455 (1957); Grovenstein and Williams, *J. Am. Chem. Soc.* **83,** 412 (1961); Zimmerman and Zweig, *J. Am. Chem. Soc.* **83,** 1196 (1961).

[56] Grovenstein and Wentworth, *J. Am. Chem. Soc.* **85,** 3305 (1963).

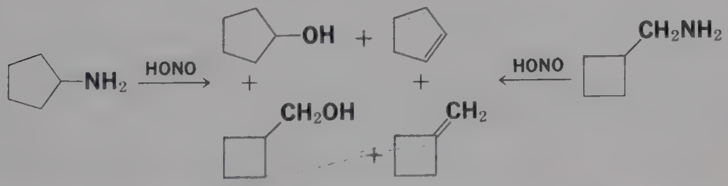
[57] For reviews, see Collins, *Quart. Rev.* (*London*) **14,** 357–377 (1960); Pocker, in Ref. 1, vol. 1, pp. 15–25.



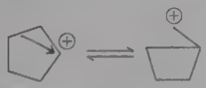
It is obvious that other compounds in which a positive charge can be placed on a carbon α to one bearing an OH group can also give this rearrangement. This is true for β-amino alcohols, which rearrange upon treatment with nitrous acid (this is called the *semipinacol* rearrangement) and iodohydrins, for which the reagent is mercuric oxide. The rearrangement is also given by compounds which are converted to 1,2-diols under the reaction conditions: especially epoxides, but also 1,2-diethers. Among the evidence for the mechanism given is that $Me_2COHCOHMe_2$, $Me_2COHCNH_2Me_2$, and $Me_2COHCClMe_2$ gave the reaction at different rates (as would be expected) but yielded the *same mixture* of two products—pinacol and pinacolone—indicating a common intermediate.[58] For a discussion of which groups preferentially migrate, see page 787.

OS **I**, 462; **II**, 73, 408; **III**, 312; **IV**, 375, 957; **41**, 53; **42**, 38.

8-3 Expansion and contraction of rings



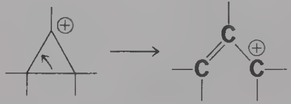
When a positive charge is formed on an alicyclic ring, then migration of an alkyl group gives ring contraction, producing a ring which is one carbon smaller than the original:



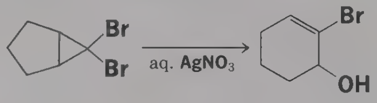
Note that this change involves conversion of a secondary to a primary carbonium ion. In a similar manner, when a positive charge is placed on a carbon α to an alicyclic ring, ring expansion may take place. The new carbonium ion, and the old one, may then give products by elimination or by combination with a nucleophile, so that this process is really a special case of reaction **8-1**. Usually both rearranged and unrearranged products are formed, so that, for example, cyclopentylamine and cyclobutylmethylamine give similar mixtures of the four products shown above, upon treatment with nitrous acid. When the carbonium ion is formed by diazotization of an amine, the reaction is called the *Demyanov rearrangement*,[59] but of course similar products are formed when the carbonium ion is generated in other ways. The expansion reaction has been performed on rings of C_3 to C_8.[60] It may be that the mixture of products, at least with some rings, arises from differences in conformation of the NH_2 group. For six-membered rings, in most cases there is a mixture of axial and equatorial NH_2 groups. When the reaction was applied to compounds with the NH_2 frozen into an axial position (by a 4-*tert*-butyl group), there was preponderately normal elimination and substitution, but compounds containing only equatorial NH_2 gave only ring contraction.[61] A positive charge generated on a three-membered ring may give "contraction" to an allylic cation:

---

[58] Pocker, *Chem. Ind.* (*London*) **1959**, 332.



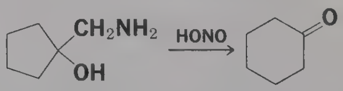
An example is the conversion of **28** to **29**:[62]



28 **29**

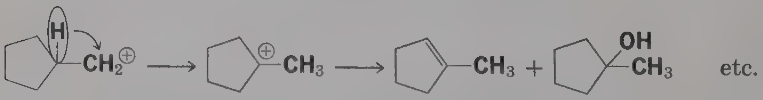
There is much evidence to show that the carbonium ion formed from a *four-membered* ring substrate is actually the same as that formed on a carbon α to a three-membered ring, in other words, a nonclassical carbonium ion (see **12**, p. 130).

Ring expansions of certain hydroxyamines, e.g.,



are analogous to the semipinacol rearrangement (**8-2**). This reaction is called the *Tiffeneu-Demyanov ring expansion*. These have been performed on rings of C_4 to C_8, and the yields are better than for the simple Demyanov ring expansion.

Besides ring expansion, carbonium ions α to a ring may undergo two other types of rearrangement: hydride shift and ring opening:



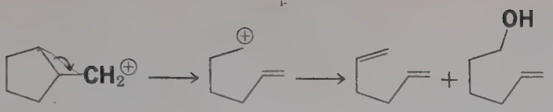
---

[59] For a review, see Smith and Baer, *Org. Reactions* **11**, 157–188 (1960).

[60] For a review concerning three- and four-membered rings, see Breslow, in Ref. 1, vol. 1, pp. 233–294.

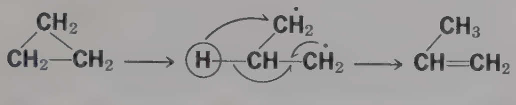
[61] Chérest, Felkin, Sicher, Šipoš, and Tichý, *J. Chem. Soc.* **1965**, 2513.

[62] Skell and Sandler, *J. Am. Chem. Soc.* **80**, 2024 (1958).

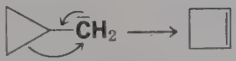


etc.

Not all ring expansion and contraction involves carbonium-ion intermediates. Upon pyrolysis, cyclopropanes undergo "contraction" to propenes. In the simplest case, cyclopropane gives propene when heated to 400–500°. The mechanism probably involves a biradical intermediate:

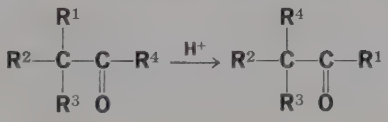


Ring expansion is also undergone by cyclopropylcarbenes, e.g.,



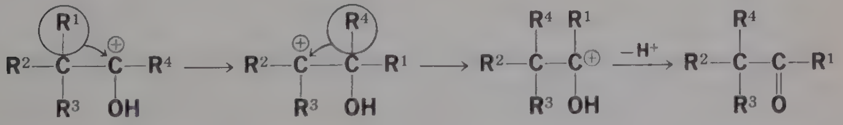
OS **III,** 276; **IV,** 221, 957; **44,** 26.

8-4 Acid-catalyzed rearrangements of aldehydes and ketones

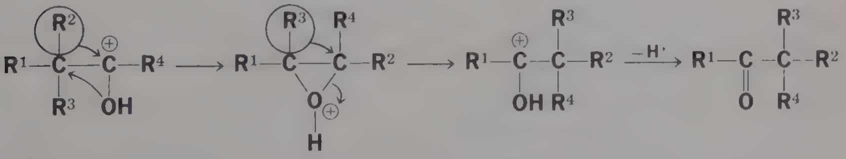


$$R^2-\underset{R^3}{\overset{R^1}{C}}-\underset{\underset{O}{\|}}{C}-R^4 \xrightarrow{H^+} R^2-\underset{R^3}{\overset{R^4}{C}}-\underset{\underset{O}{\|}}{C}-R^1$$

Rearrangements of this type, where a group α to a carbonyl "changes places" with a group attached to the carbonyl carbon, occur when migratory aptitudes are favorable. There are two mechanisms, each beginning with protonation of the oxygen and each involving two migrations. In one mechanism the migrations are in opposite directions:[63]



In the other pathway, there is an epoxide (protonated) intermediate, and the migrations are in the same direction:[64]

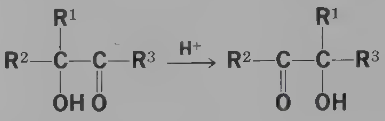


---

[63] Rothrock and Fry, *J. Am. Chem. Soc.* **80,** 4349 (1958).

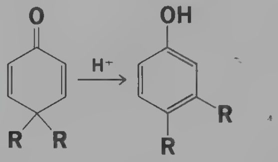
[64] Favorskii and Chilingaren, *Compt. rend.* **182,** 221 (1926).

If the reaction is carried out with ketone labeled in the C=O group with ^{14}C, then the first pathway predicts that the product should contain all the ^{14}C in the C=O carbon, while in the second pathway the label should be in the α-carbon. It has been shown that both carbons were labeled, indicating the presence of both pathways.[65] Rearrangements have been demonstrated when R^2 and R^3 were hydrogen, as well as alkyl.[66] With α-hydroxy aldehydes and ketones, the process stops after only one migration:

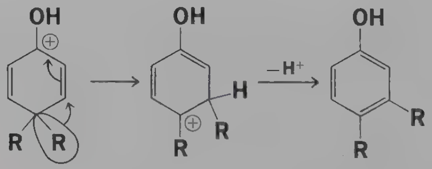


$$\mathrm{R^2{-}\overset{\displaystyle R^1}{\underset{\displaystyle OH}{C}}{-}\underset{\displaystyle O}{\overset{\|}{C}}{-}R^3 \xrightarrow{H^+} R^2{-}\underset{\displaystyle O}{\overset{\|}{C}}{-}\overset{\displaystyle R^1}{\underset{\displaystyle OH}{C}}{-}R^3}$$

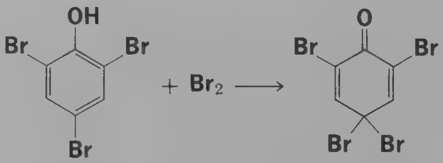
8-5 The dienone-phenol rearrangement



Compounds in which a cyclohexadienone has two alkyl groups in the 4-position undergo, upon acid treatment, migration of one of these groups to a position allylic to the carbonium ion generated by protonation of the oxygen:



The driving force in the overall reaction (the *dienone-phenol rearrangement*) is of course creation of an aromatic system. The anthrasteroid rearrangement (p. 797) is closely related. Sometimes, in the reaction of a phenol with an electrophile, a kind of reverse rearrangement (called the *phenol-dienone rearrangement*) takes place, though without an actual migration.[67] An example is



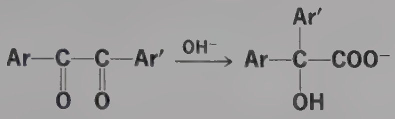
---

[65] Remizova and Zalesskaya, *J. Gen. Chem. USSR* **34**, 1398 (1964); Zalesskaya and Remizova, *J. Gen. Chem. USSR* **35**, 29 (1965).

[66] Fry, Eberhardt, and Ookuni, *J. Org. Chem.* **25**, 1252 (1960).

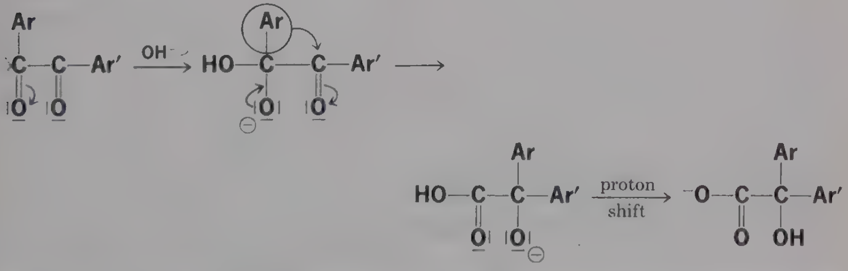
[67] For a review, see Ershov, Volod'kin, and Bogdanov, *Russ. Chem. Rev.* **32**, 75–93 (1963).

8-6 The benzil-benzilic acid rearrangement



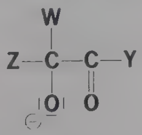
$$\text{Ar—CO—CO—Ar}' \xrightarrow{\text{OH}^-} \text{Ar—C(Ar}')\text{(OH)—COO}^-$$

When treated with base, α-diketones rearrange to give the salts of α-hydroxy acids, a reaction known as the *benzil-benzilic acid rearrangement* (benzil is PhCOCOPh; benzilic acid is $Ph_2COHCOOH$).[68] Although the reaction is usually illustrated with aryl groups, it may also be applied to aliphatic diketones and to α-keto acids. The use of alkoxide ion instead of OH^- gives the corresponding ester directly,[69] though alkoxide ions which are readily oxidized (such as OEt^- or $OCHMe_2^-$) are not useful here since they reduce the benzil to a benzoin. Aroxide ions (OAr^-) are not strong enough bases for the reaction. The mechanism is similar to the rearrangements in reactions **8-1** to **8-5**, but there is a difference: the migrating group does not move to a carbon with an open sextet. The carbon has an octet but can still accept a group with its pair of electrons by releasing a π pair of electrons from the C=O bond to the oxygen. The first step is attack of the base at the carbonyl group, the same as the first step of the tetrahedral mechanism of nucleophilic substitution (p. 274) and of many additions to the C=O bond (Chapter 16):



The mechanism has been intensively studied, and there is much evidence for it.[68] The reaction is irreversible.

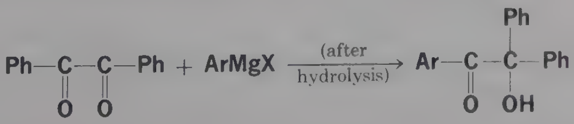
There are other related reactions in which an intermediate of the form



$$\text{Z—C(W)(O}^-\text{)—CO—Y}$$

30

is formed and then rearrangement follows. An example is



$$\text{Ph—CO—CO—Ph} + \text{ArMgX} \xrightarrow[\text{hydrolysis)}]{\text{(after}} \text{Ar—CO—C(Ph)(OH)—Ph}$$

---

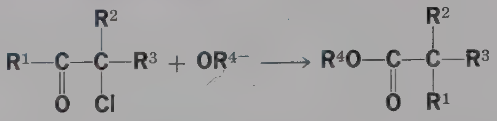
[68] For a review, see Selman and Eastham, *Quart. Rev.* (*London*) **14**, 221–235 (1960).

[69] Doering and Urban, *J. Am. Chem. Soc.* **78**, 5938 (1956).

In the intermediate **30**, for the benzilic acid rearrangement, Z = OH, W and Y = R, Ar, or H; for the benzilic ester case, Z = OR, W and Y = R or Ar; for the Grignard example shown, Z, W, and Y all = Ar. In other cases, W and Z may be ArNH, ArCO, RCO, etc., and Y may be OH, RCO, etc.

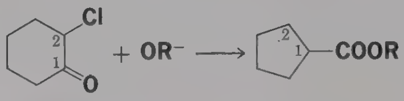
OS **I**, 89.

8-7 The Favorskii rearrangement



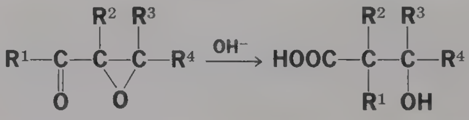
$$R^1{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R^2}{|}}{\underset{\underset{Cl}{|}}{C}}{-}R^3 + OR^{4-} \longrightarrow R^4O{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R^2}{|}}{\underset{\underset{R^1}{|}}{C}}{-}R^3$$

The reaction of α-halo ketones (chloro or bromo) with alkoxide ions to give rearranged esters is called the *Favorskii rearrangement.*[70] The use of hydroxide ions or amines as bases leads to the free acid (salt) or amide, respectively, instead of the ester. Cyclic α-halo ketones give ring contraction:



31 **32**

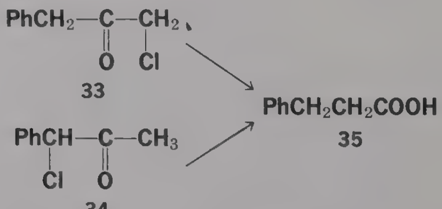
The reaction has also been carried out on α,β-epoxy ketones:[71]



$$R^1{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R^2}{|}}{C}{-}\overset{\overset{R^3}{|}}{C}{-}R^4 \xrightarrow{OH^-} HOOC{-}\overset{\overset{R^2}{|}}{\underset{\underset{R^1}{|}}{C}}{-}\overset{\overset{R^3}{|}}{\underset{\underset{OH}{|}}{C}}{-}R^4$$

The fact that an epoxide gives a reaction analogous to a halide indicates that the oxygen and halogen are leaving groups in a nucleophilic substitution step.

Through the years the mechanism of the Favorskii rearrangement has been the subject of much investigation, and at least five different mechanisms have been proposed. However, the finding that **33** and **34** *both* give **35**



$$PhCH_2{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{Cl}{|}}{CH_2}$$

33

$$PhCH_2CH_2COOH$$

35

$$\underset{\underset{Cl}{|}}{PhCH}{-}\underset{\underset{O}{\|}}{C}{-}CH_3$$

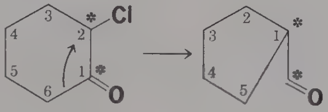
34

---

[70] For a review, see Kende, *Org. Reactions* **11**, 261–316 (1960).

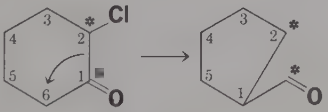
[71] House and Gilmore, *J. Am. Chem. Soc.* **83**, 3972 (1961).

(this behavior is typical) shows that any mechanism where the halogen leaves and R^1 takes its place is invalid, since in such a case **33** would be expected to give **35** (with $PhCH_2$ migrating), but **34** should give PhCHMeCOOH (with CH_3 migrating). That is, in the case of **34**, it was PhCH that migrated and not methyl. Another important result was determined by radioactive labeling. **31**, in which C-1 and C-2 were equally labeled with ^{14}C, was converted to **32**. The product was found to contain 50% of the label on the carbonyl carbon, 25% on C-1 and 25% on C-2.[72] Now the carbonyl carbon, which originally carried half of the radioactivity, still had this much, so that the rearrangement did not directly affect *it*. However, if the C-6 carbon had migrated to C-2, then the other half of the radioactivity would be only on C-1 of the product:



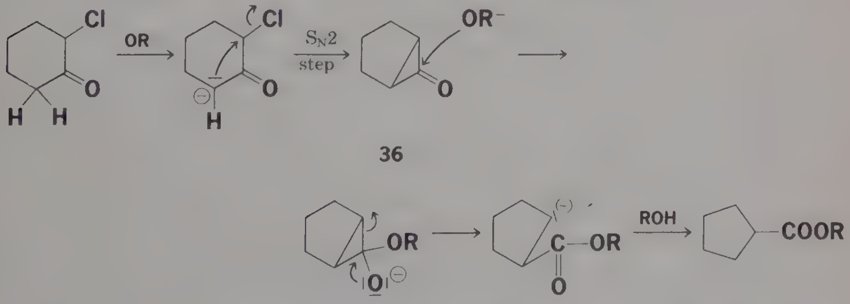
31

On the other hand, if the migration had gone the other way—if the C-2 carbon had migrated to C-6—then this half of the radioactivity would be found solely on C-2 of the product:



31

The fact that C-1 and C-2 were found to be equally labeled showed that *both migrations were occurring*, and with equal probability. Since C-2 and C-6 of **31** are not equivalent, this means that there must be a symmetrical intermediate. The type of intermediate which best fits the circumstances is a cyclopropanone, and the mechanism would be formulated:



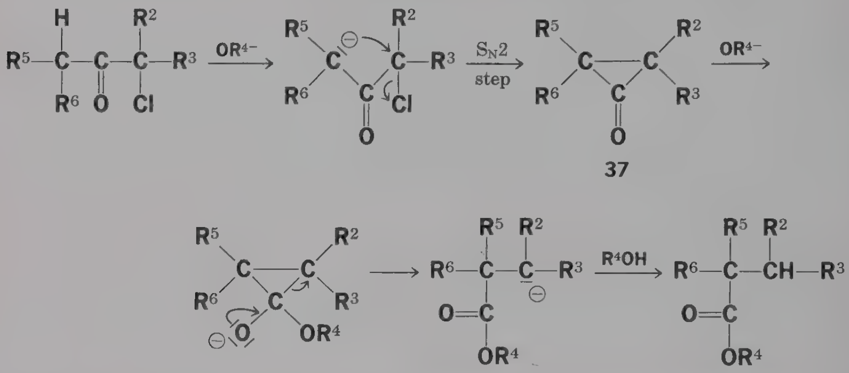
36

A preliminary migration of the chlorine from C-2 to C-6 was ruled out by the fact that recovered **31** had the same isotopic distribution as the starting **31**.

---

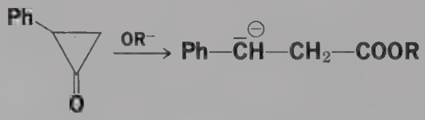
[72] Loftfield, *J. Am. Chem. Soc.* **73**, 4707 (1951).

For the general case the mechanism would be (replacing R^1 of our former symbolism with CHR^5R^6, since it is obvious that for this mechanism an α hydrogen is required on the nonhalogenated side of the carbonyl):



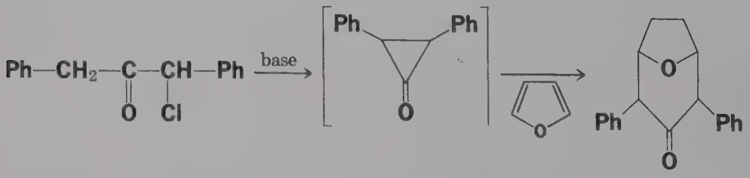
37

36 is a symmetrical compound, and the three-membered ring may be opened with equal probability on either side of the carbonyl, accounting for the results with ^{14}C. In the general case, **37** is not symmetrical and should open on the side which gives the more stable carbanion. This accounts for the fact that **33** and **34** give the same product. The intermediate in both cases



38

is **38,** which always opens to give the carbanion stabilized by resonance. The cyclopropanone intermediate (**37**) has not been isolated, but it has been trapped, as an adduct with furan, in a sort of Diels-Alder reaction:[73]



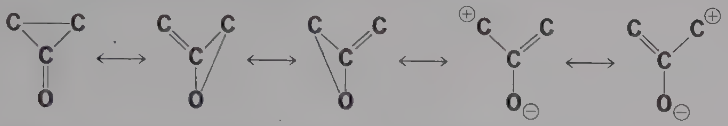
and in another way.[74] In one case (that of tetramethylcyclopropanone), **37** has been synthesized by another method and shown to yield Favorskii products upon treatment with NaOMe.[75] The hemiacetal of tetramethylcyclopropanone gave the same products. It has been proposed that **37** is stabilized by resonance of the following type:[76]

---

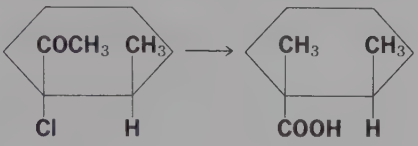
[73] Fort, *J. Am. Chem. Soc.* **84**, 4979 (1962); Cookson and Nye, *Proc. Chem. Soc.* **1963**, 129.

[74] Breslow, Posner, and Krebs, *J. Am. Chem. Soc.* **85**, 234 (1963).

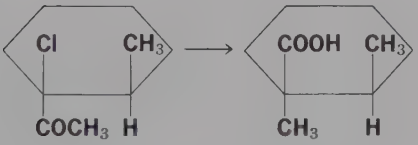
[75] Turro and Hammond, *J. Am. Chem. Soc.* **87**, 3258 (1965).



Additional evidence for the mechanism is the finding that the diastereomers **39** and **40** reacted stereospecifically, to give, respectively, **41** and **42**:[77]



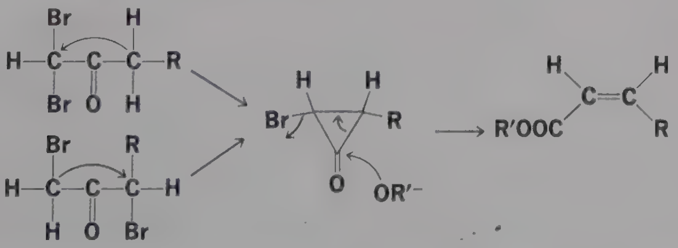
39 **41**



40 **42**

This result demonstrated that the carbon attached to the chlorine underwent inversion, as required by the S_N2 step. There is evidence that the S_N2 step is the slow step of the reaction.[78]

When the Favorskii rearrangement is applied to α,α-dihalo ketones containing an α' hydrogen[79] or to α,α'-dihalo ketones containing an α hydrogen,[80] the product is an α,β-unsaturated ester. This reaction is stereoselective and gives the cis olefin. In either case the same cyclopropanone is formed. Ring opening is different here, involving simultaneous elimination of halide ion:



---

[76] Fort, *J. Am. Chem. Soc.* **84,** 2620, 2625 (1962); House and Gilmore, *J. Am. Chem. Soc.* **83,** 3980 (1961).

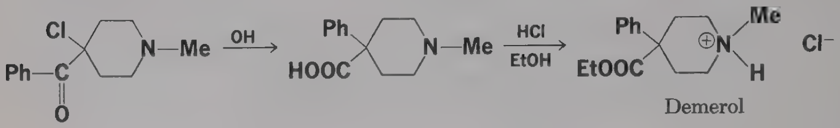
[77] Stork and Borowitz, *J. Am. Chem. Soc.* **82,** 4307 (1960); House and Gilmore, *J. Am. Chem. Soc.* **83,** 3980 (1961). See also Smissman, Lemke, and Kristiansen, *J. Am. Chem. Soc.* **88,** 334 (1966).

[78] Charpentier-Morize, Mayer, and Tchoubar, *Bull. Soc. chim. France* **1965,** 529.

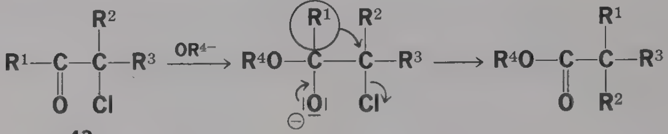
[79] Kennedy, McCorkindale, Raphael, Scott, and Zwanenburg, *Proc. Chem. Soc.* **1964,** 148.

[80] Rappe and Adeström, *Acta Chem. Scand.* **19,** 383 (1965); Rappe, *Acta Chem. Scand.* **20,** 862 (1966).

The mechanism discussed is in accord with all the facts when the halo ketone contains an α hydrogen on the other side of the carbonyl group. However, ketones which do not have a hydrogen there also rearrange to give the same type of product. This is usually called the *quasi-Favorskii rearrangement*. An example is found in the preparation of demerol:[81]

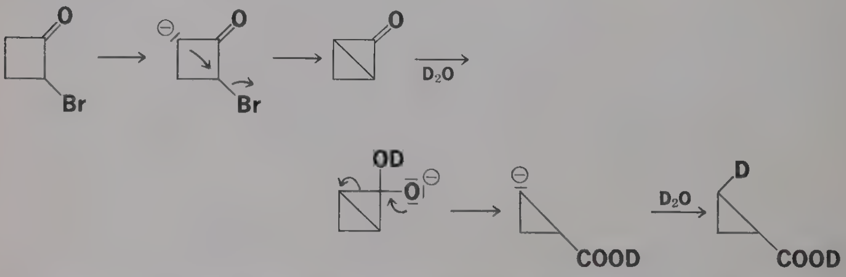


In this case the mechanism may be similar to that of reaction **8-6**:

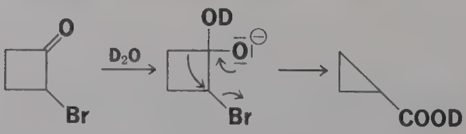


43

However, it was shown that racemization and not inversion takes place when an optically active **43** is used, an observation which casts doubt on this mechanism (called the *semibenzilic mechanism*).[82] It has been shown that, even where there *is* an appropriately situated α hydrogen, the mechanism is not necessarily the cyclopropanone one. 2-Bromocyclobutanone gives the Favorskii rearrangement to yield cyclopropanecarboxylic acid (**44**) when treated with water; a stronger base is not necessary. When D_2O was used as the reagent, the **44** isolated was not labeled in the ring, all the deuterium appearing as COOD.[83] If the cyclopropanone mechanism were operating, deuterium would also be found in the ring:



On the other hand, the semibenzilic mechanism correctly predicts the product:



44

---

[81] Smissman and Hite, *J. Am. Chem. Soc.* **81**, 1201 (1959).

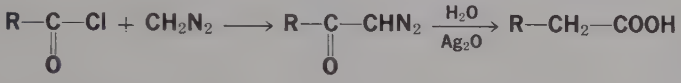
[82] Smissman and Diebold, *J. Org. Chem.* **30**, 4005 (1966).

[83] Conia and Salaün, *Tetrahedron Letters* **1963**, 1175; *Bull. Soc. chim. France* **1964**, 1957.

It may be that the cyclopropanone mechanism does not operate in this case because of the strain in the bicyclobutanone ring system.

OS **IV,** 594.

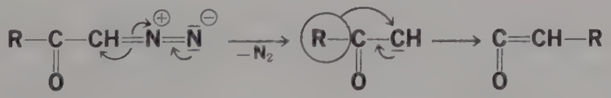
8-8 The Arndt-Eistert synthesis



$$\mathrm{R{-}\underset{\overset{\|}{O}}{C}{-}Cl + CH_2N_2 \longrightarrow R{-}\underset{\overset{\|}{O}}{C}{-}CHN_2 \xrightarrow[Ag_2O]{H_2O} R{-}CH_2{-}COOH}$$

In the *Arndt-Eistert synthesis* an acyl halide is converted to a carboxylic acid with one additional carbon.[84] The first step of this process is reaction **0-97.** The actual rearrangement occurs in the second step, upon treatment of the diazoketone with water and silver oxide. This rearrangement is called the *Wolff rearrangement.* It is the best method of increasing a carbon chain by one if a *carboxylic acid* is available (reactions **0-88,** p. 361, and **6-34,** p. 689, begin with alkyl halides). If an alcohol R′OH is used instead of water, the ester RCH_2COOR' is isolated directly. Similarly, ammonia gives the amide. Other catalysts are sometimes used, e.g., colloidal platinum, copper, etc., but sometimes heat is enough. Of course diazoketones prepared in any other way also give the rearrangement. The reaction is of wide scope. R may be alkyl or aryl and may contain many functional groups including unsaturation, but not including groups acidic enough to react with CH_2N_2 or diazoketones (e.g., reactions **0-6,** p. 306, and **0-28,** p. 324). Sometimes the reaction is performed with other diazoalkanes (that is, $R'CHN_2$) to give RCHR′COOH.

The mechanism is generally regarded to involve formation of a carbene. It is the divalent carbon which has the open sextet and to which the migrating group brings its electron pair:



$$\mathrm{R{-}\underset{\overset{\|}{O}}{C}{-}CH{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} \xrightarrow[-N_2]{} R{-}\underset{\overset{\|}{O}}{C}{-}CH \longrightarrow \underset{\overset{\|}{O}}{C}{=}CH{-}R}$$

HO H
| |
O=C -C -R

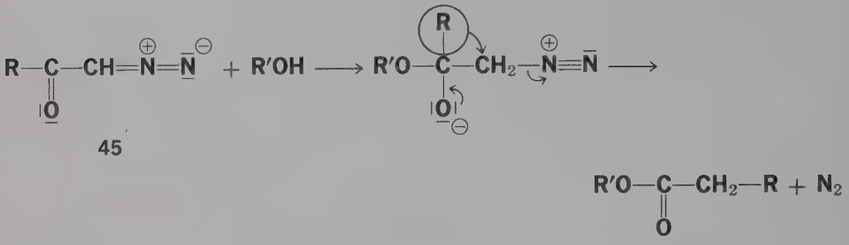
OR H
O-C -C -

HN H
)-, (

The actual product of the reaction is thus the ketene, which then reacts with water (reaction **5-2,** p. 581), an alcohol (reaction **5-5,** p. 584), or ammonia or an amine (reaction **5-9,** p. 589). The purpose of the catalyst is not well understood, though many suggestions have been made. This mechanism is strictly analogous to that of the Curtius rearrangement (reaction **8-16**). Although the mechanism as shown above involves a free carbene, it has never been proved that a free carbene is present. It may well be that the two steps are concerted and that a free carbene is not involved. Indeed, it is even possible that a ketene is not involved either. It has been argued that the water (or alcohol or amine) attacks the diazo ketone directly and that the mechanism is (illustrated for an alcohol):[85]

---

[84] For reviews, see Bachmann and Struve, *Org. Reactions* **1,** 38–62 (1942); Eistert, in "Newer Methods of Preparative Organic Chemistry," vol. 1, pp. 513–570, Interscience Publishers, Inc., New York, 1948; Weygand and Bestmann, in Foerst, "Newer Methods of Preparative Organic Chemistry," vol. 3, pp. 451–508, Academic Press Inc., New York, 1964 [this article also appeared in *Angew. Chem.* **72,** 535–554 (1960)]; Smith, in Ref. 1, pp. 528–550, 558–564.

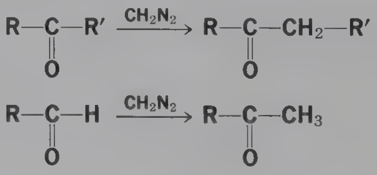


45

If this is true, then the mechanism is not analogous to that of reaction **8-16.** It was precisely this consideration which was taken as evidence for the nonketene mechanism: in the case of **45** (R = Ph_3C), the normal rearrangement product was not obtained; although Curtius rearrangement of the corresponding azide did give the normal product.[85] However, particularly stable ketenes (for example, $Ph_2C{=}C{=}O$) have been isolated, and more reactive ketenes have been trapped as β-lactams (reaction **6-66,** p. 724).[86]

OS **III,** 356.

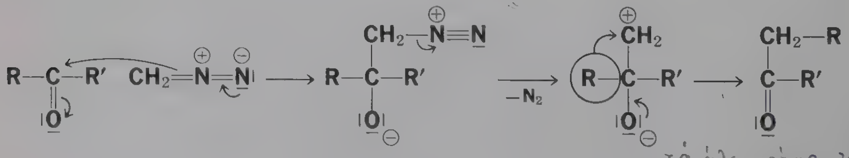
8-9 Homologization of aldehydes and ketones



$$R{-}\underset{\underset{O}{\|}}{C}{-}R' \xrightarrow{CH_2N_2} R{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}R'$$

$$R{-}\underset{\underset{O}{\|}}{C}{-}H \xrightarrow{CH_2N_2} R{-}\underset{\underset{O}{\|}}{C}{-}CH_3$$

Aldehydes and ketones may be converted to their homologs with diazomethane.[87] Formation of the epoxide (reaction **6-62,** p. 720) is a side reaction. Although this reaction appears superficially to be similar to the insertion of carbenes into C—H bonds (reaction **2-11,** p. 466), the mechanism is quite different, and this reaction is a true rearrangement. No free carbene is involved. The first step is an addition to the C=O bond of the aldehyde or ketone:



46 47

τὰ ἠλεκτρόνια τοῦ Ο
κινοῦνται – σχηματίζε

---

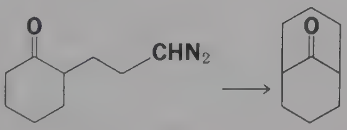
[85] Wilds, Woolsey, Van Den Berghe, and Winestock, *Tetrahedron Letters* **1965**, 4481; following a suggestion of Eistert (Ref. 84).

[86] Kirmse and Horner, *Chem. Ber.* **89**, 2759 (1956); also see Horner and Spietschka, *Chem. Ber.* **89**, 2765 (1956).

[87] For reviews, see Gutsche, *Org. Reactions* **8**, 364–429 (1954); Eistert, Ref. 84, pp. 521–537.

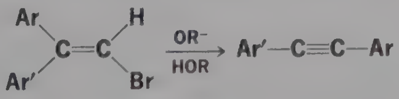
The betaine **46** can sometimes be isolated. As shown on page 721, **47** can also go to the epoxide. The evidence for this mechanism is summarized in the review by Gutsche.[87] It may be noted that this mechanism is essentially the same as in the apparent "insertions" of oxygen (reaction **8-20**) and nitrogen (reaction **8-18**) into ketones. Although the mechanism normally does not involve a free carbene, it has been shown that free carbene does give similar products. Thus, acetone, treated with carbene, gave methyl ethyl ketone (undoubtedly by insertion into the C—H bond) and 1,1-dimethylethylene oxide.[88]

Aldehydes give fairly good yields of methyl ketones; that is, hydrogen migrates in preference to alkyl. The most abundant side product is not the homologous aldehyde, but the epoxide. However, the yield of aldehyde at the expense of methyl ketone may be increased by the addition of methanol. If the aldehyde contains electron-withdrawing groups, the yield of epoxides is increased, and the ketone is formed in smaller amounts, if at all. Ketones give poorer yields of homologous ketones. Epoxides are usually the predominant product here, especially when one or both R groups contains an electron-withdrawing group. The yield of ketones also decreases with increasing length of the chain. The use of boron trifluoride[89] or aluminum chloride[90] increases the yield of ketone. Cyclic ketones behave particularly well and give good yields of ketones with the ring expanded by one. Aliphatic diazo compounds ($RCHN_2$ and R_2CN_2) are sometimes used instead of diazomethane, with the expected results.[91] An interesting example is the preparation of bicyclic compounds from alicyclic compounds with a diazo group in the side chain, e.g.,[92]



OS **IV**, 225, 780.

8-10 The Fritsch-Buttenberg-Wiechell rearrangement


$$Ar(Ar')C{=}CHBr \xrightarrow[HOR]{OR^-} Ar'{-}C{\equiv}C{-}Ar$$

The rearrangement of 1,1-diaryl-2-haloethylenes to diarylacetylenes with strong bases is called the *Fritsch-Buttenberg-Wiechell rearrangement* (sometimes the *Fritsch rearrangement,* though this is unjust, since the three workers discovered it independently in 1894[93]).[94] Alkoxide ions, sodium amide, and alkyl- and aryllithiums have been used as bases. The order of halide reactivity is Br > I ≫ Cl.[95] There are two main side reactions, which may predominate. One of these is simple nucleophilic substitution of the halide by the base (for example, $Ar_2C{=}CHBr + OEt^- \longrightarrow Ar_2C{=}CHOEt$), and the other, which occurs with alkyl- and aryllithiums, is halogen-metal interchange (reaction **2-25,** p. 476). In the latter case the olefin goes to $Ar_2C{=}CHLi$, which may be converted to $Ar_2C{=}CHCOOH$ with CO_2 or to $Ar_2C{=}CH_2$ with water. The reaction has also been applied to compounds of the type $ArRC{=}CHBr$, but $R_2C{=}CHBr$ do not generally give the rearrangement.

---

[88] Bradley and Ledwith, *J. Chem. Soc.* **1963**, 3480.

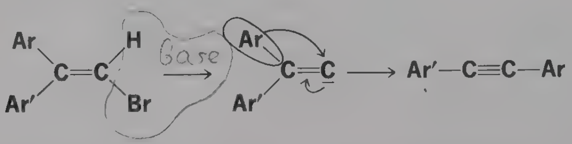
[89] House, Grubbs, and Gannon, *J. Am. Chem. Soc.* **82**, 4099 (1960).

[90] Müller and Heischkeil, *Tetrahedron Letters* **1964**, 2809.

[91] For example, see Smith, *J. Org. Chem.* **25**, 453 (1960); Warner, Walsh, and Smith, *J. Chem. Soc.* **1962**, 1232.

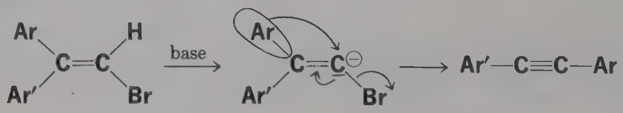
[92] Gutsche and Bailey, *J. Org. Chem.* **28**, 607 (1963); Bailey, Bowers, and Gutsche, *J. Org. Chem.* **28**, 610 (1963).

In this rearrangement, a hydrogen and a halogen are removed from the same carbon upon treatment with a base, and it is tempting to assume that a carbene intermediate is involved here (see p. 163):



However, a major piece of evidence against this mechanism is that the reaction is stereoselective: the predominant migrating group is the one trans to the halogen. This was determined by the use of two different aryl groups and the labeling of one of the ethylenic carbons with ^{14}C.[96] A free carbene should be symmetrical, and it should not matter which group migrates.[97] Other evidence against the carbene mechanism is that products of carbene insertion or addition are not found. If we reject the carbene mechanism, there are still two major possibilities.[98] The aryl group may migrate with (mechanism *a*) or without (mechanism *b*) its electrons:

Mechanism *a*



48

---

[93] Fritsch, *Ann.* **279,** 319 (1894); Buttenberg, *Ann.* **279,** 327 (1894); Wiechell, *Ann.* **279,** 337 (1894).

[94] For a review, see Köbrich, *Angew. Chem. Intern. Ed. Engl.* **4,** 49–68 (1965), pp. 63–67.

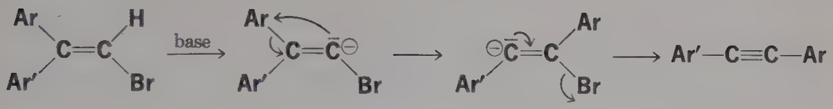
[95] Pritchard and Bothner-By, *J. Phys. Chem.* **64,** 1271 (1960).

[96] Curtin, Flynn, and Nystrom, *J. Am. Chem. Soc.* **80,** 4599 (1958); Bothner-By, *J. Am. Chem. Soc.* **77,** 3293 (1955).

[97] It has been shown (Tadros, Sakla, Ishak, and Armanious, *J. Chem. Soc.* **1963,** 4218) that the reaction of 1-phenyl-1-*p*-anisyl-2-bromoethylene with sodium glycoxide in boiling ethylene glycol is not stereoselective, the anisyl group preferentially migrating, whether cis or trans. It may be that the mechanism in this case is different, or more simply, that here the olefin isomerized before migration took place.

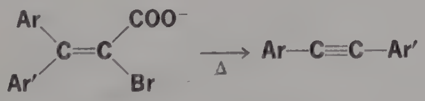
[98] An *intermolecular* mechanism was ruled out by crossover experiments and by the fact that a substituent on a migrating ring is found in the same position in the product.

Mechanism *b*



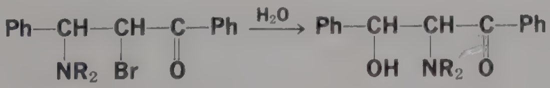
Although we have shown these mechanisms with two and three steps, respectively, it is also possible that two or three of the steps are concerted. The principal way of distinguishing between mechanisms *a* and *b* is the study of the effects of substituents on the migrating group. In mechanism *a* the reaction with respect to the migrating group is electrophilic aromatic substitution, with a transition state in which the ring is positively charged. Electron-donating substituents in the ortho or para positions should aid the migration, and withdrawing substituents should hinder it. In mechanism *b* the reaction is nucleophilic aromatic substitution, with a negatively charged transition state, and the effect of substituents should be just the opposite. The results are in accord with mechanism *a*.[99] The question remains as to whether it is a one-step or two-step process. There is evidence that, at least in some cases, there is a two-step mechanism: the intermediate **48** has been isolated as the lithium salt, and on heating gave the diarylacetylene;[100] and hydrogen-deuterium exchange has been shown.[95] However, it may be that in other cases the two steps are concerted. The fact that the reaction is stereoselective does not *require* that the reaction be concerted, since vinyl carbanions can hold their configurations (p. 147).

A similar rearrangement has been carried out on salts of 3,3-diaryl-2-halopropenoic acids:[101]



B. Carbon-to-carbon migrations of other groups

8-11 Migrations of halogen, hydroxyl, amino, etc.



$$\underset{\substack{|\\ NR_2}}{Ph-CH}-\underset{\substack{|\\ Br}}{CH}-\underset{\substack{\|\\ O}}{C}-Ph \xrightarrow{H_2O} \underset{\substack{|\\ OH}}{Ph-CH}-\underset{\substack{|\\ NR_2}}{CH}-\underset{\substack{\|\\ O}}{C}-Ph$$

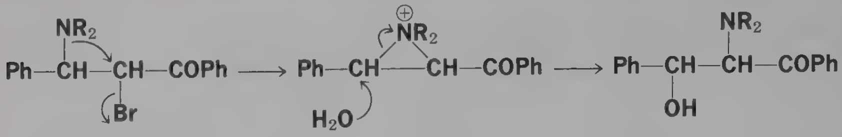
When a nucleophilic substitution is carried out on a substrate which has a neighboring group (p. 263) on the adjacent carbon, then if the intermediate is opened on the opposite side, the result is migration of the neighboring group. In the example shown above (NR_2 = morpholino)[102] the reaction took place as follows:

---

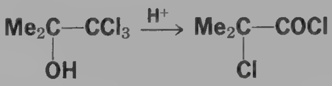
[99] Köbrich and Trapp, *Z. Naturforsch.* **18b**, 1125 (1963), *Chem. Ber.* **99**, 680 (1966); Jones and Damico, *J. Am. Chem. Soc.* **85**, 2273 (1963); Köbrich, Trapp, and Hornke, *Tetrahedron Letters* **1964**, 1131.

[100] Köbrich and Trapp, Ref. 99.

[101] Köbrich and Fröhlich, *Chem. Ber.* **98**, 3637 (1965).

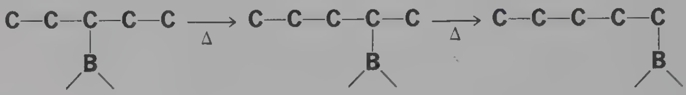


Another example is[103]



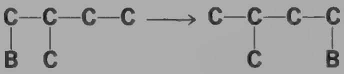
$$\mathrm{Me_2}\underset{\substack{|\\ \mathrm{OH}}}{\mathrm{C}}\mathrm{-CCl_3} \xrightarrow{\mathrm{H^+}} \mathrm{Me_2}\underset{\substack{|\\ \mathrm{Cl}}}{\mathrm{C}}\mathrm{-COCl}$$

8-12 Migration of boron



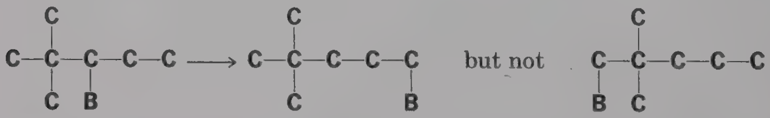
$$\mathrm{C-C-}\underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}}\mathrm{-C-C} \xrightarrow[\Delta]{} \mathrm{C-C-C-}\underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}}\mathrm{-C} \xrightarrow[\Delta]{} \mathrm{C-C-C-C-}\underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}}$$

When a nonterminal borane is heated at temperatures ranging from 100 to 200°, the boron moves toward the end of the chain.[104] The reaction is catalyzed by small amounts of diborane or other species containing B—H bonds. The boron can move past a branch, e.g.,



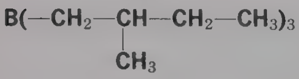
$$\underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}}\mathrm{-}\underset{\substack{|\\ \mathrm{C}}}{\mathrm{C}}\mathrm{-C-C} \longrightarrow \mathrm{C-}\underset{\substack{|\\ \mathrm{C}}}{\mathrm{C}}\mathrm{-C-}\underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}}$$

but not past a double branch, e.g.,



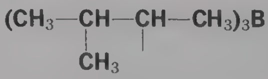
$$\mathrm{C-}\overset{\substack{\mathrm{C}\\ |}}{\underset{\substack{|\\ \mathrm{C}}}{\mathrm{C}}}\mathrm{-}\underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}}\mathrm{-C-C} \longrightarrow \mathrm{C-}\overset{\substack{\mathrm{C}\\ |}}{\underset{\substack{|\\ \mathrm{C}}}{\mathrm{C}}}\mathrm{-C-C-}\underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}} \quad \text{but not} \quad \underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}}\mathrm{-}\overset{\substack{\mathrm{C}\\ |}}{\underset{\substack{|\\ \mathrm{C}}}{\mathrm{C}}}\mathrm{-C-C-C}$$

The reaction is an equilibrium: **49, 50,** and **51** each gave a mixture containing about 40% **49,** 1% **50,** and 59% **51.** The migration can go quite a long



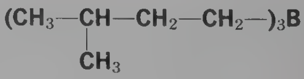
$$\mathrm{B(-CH_2-}\underset{\substack{|\\ \mathrm{CH_3}}}{\mathrm{CH}}\mathrm{-CH_2-CH_3)_3}$$

49



$$\mathrm{(CH_3-}\underset{\substack{|\\ \mathrm{CH_3}}}{\mathrm{CH}}\mathrm{-}\underset{|}{\mathrm{CH}}\mathrm{-CH_3)_3B}$$

50



$$\mathrm{(CH_3-}\underset{\substack{|\\ \mathrm{CH_3}}}{\mathrm{CH}}\mathrm{-CH_2-CH_2-)_3B}$$

51

---

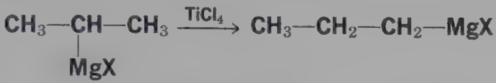
[102] Southwick and Walsh, *J. Am. Chem. Soc.* **77**, 405 (1955).

[103] Kundiger, Ikenberry, Ovist, Peterson, and Dick, *J. Am. Chem. Soc.* **82**, 2953 (1960).

[104] Brown, "Hydroboration," pp. 136–149, W. A. Benjamin, Inc., New York, 1962; Brown and Zweifel, *J. Am. Chem. Soc.* **88**, 1433 (1966).

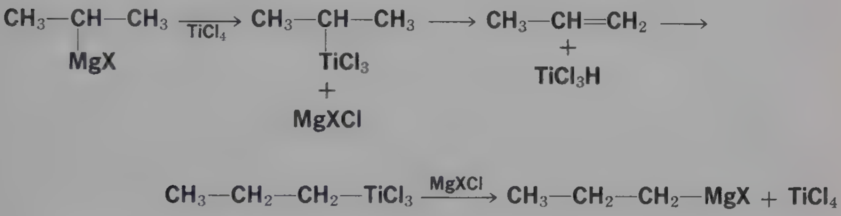
distance. Thus $(C_{11}H_{23}CHC_{11}H_{23})_3B$ could be completely converted to $(C_{23}H_{47})_3B$, involving a migration of 11 positions.[105] The reaction is useful for the migration of double bonds in a controlled way (see reaction **2-2,** p. 453). The mechanism probably involves elimination-addition (see reactions **7-16,** p. 766, and **5-13,** p. 599).

8-13 Rearrangement of Grignard reagents



$$CH_3{-}\underset{\displaystyle MgX}{CH}{-}CH_3 \xrightarrow{TiCl_4} CH_3{-}CH_2{-}CH_2{-}MgX$$

The MgX of Grignard reagents can migrate to terminal positions in the presence of small amounts of $TiCl_4$.[106] The mechanism proposed consists in metal exchange (reaction **2-21,** p. 474), elimination-addition, and metal exchange:

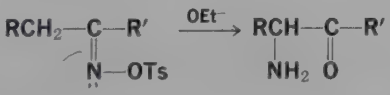


$$CH_3{-}\underset{\displaystyle MgX}{CH}{-}CH_3 \xrightarrow[TiCl_4]{} \underset{\displaystyle MgXCl}{\underset{+}{CH_3{-}\underset{\displaystyle TiCl_3}{CH}{-}CH_3}} \longrightarrow \underset{\displaystyle TiCl_3H}{\underset{+}{CH_3{-}CH{=}CH_2}} \longrightarrow$$

$$CH_3{-}CH_2{-}CH_2{-}TiCl_3 \xrightarrow{MgXCl} CH_3{-}CH_2{-}CH_2{-}MgX + TiCl_4$$

The addition step is similar to reaction **5-13** (p. 599) and follows Markovnikov's rule, so that the positive titanium goes to the terminal carbon.

8-14 The Neber rearrangement



$$RCH_2{-}\underset{\displaystyle \overset{..}{N}{-}OTs}{\overset{}{\underset{\|}{C}}}{-}R' \xrightarrow{OEt^-} RCH{-}\underset{}{C}{-}R' \quad \text{with } NH_2 \text{ on } CH,\ O \text{ on } C$$

α-Amino ketones may be prepared by treatment of ketoxime tosylates with a base such as ethoxide ion or pyridine.[107] This is called the *Neber rearrangement.* R is usually aryl, though the reaction has been carried out with R = alkyl or hydrogen too. R′ may be alkyl or aryl but not hydrogen. The Beckmann rearrangement (reaction **8-19**) and the abnormal Beckmann reaction (elimination to the nitrile, reaction **7-31,** p. 776) may be side reactions, though these generally occur in acid media. A similar rearrangement is given by N,N-dichloroamines of the type $RCH_2CH(NCl_2)R'$, where the product is also $RCH(NH_2)COR'$.[108] The mechanism of the Neber rearrangement is as follows:[109]

---

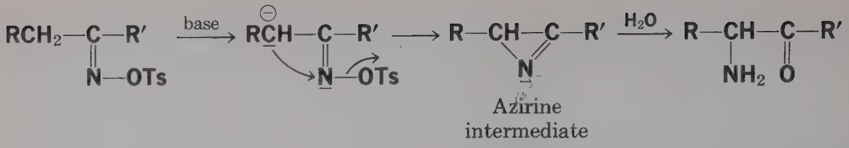
[105] Logan, *J. Org. Chem.* **26,** 3657 (1961).

[106] Cooper and Finkbeiner, *J. Org. Chem.* **27,** 1493 (1962).

[107] For a review, see O'Brien, *Chem. Rev.* **64,** 81–89 (1964).

[108] Baumgarten and Petersen, *J. Am. Chem. Soc.* **82,** 459 (1960), and references cited therein.

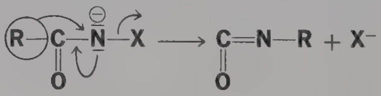
[109] Cram and Hatch, *J. Am. Chem. Soc.* **75,** 33 (1953); Hatch and Cram, *J. Am. Chem. Soc.* **75,** 38 (1953).



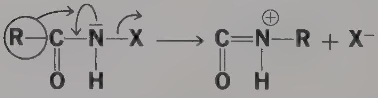
The best evidence for this mechanism is that the azirine intermediate has been isolated.[110] In contrast to the Beckmann rearrangement, this one is sterically indiscriminate:[111] both a syn and an anti ketoxime give the same product. Where there are two possible C—H groups to which the nitrogen can migrate, the more acidic proton is lost. The mechanism as shown above consists of three steps, the last being hydrolysis of an imine (reaction **6-2,** p. 656). However, it is possible that the first two steps are concerted, and it is also possible that what is shown as the second step is actually two steps: loss of OTs to give a nitrene, and formation of the azirine. In the case of the dichloroamines, HCl is first lost to give $\mathrm{RCH_2}\underset{\mathrm{NCl}}{\underset{\|}{\mathrm{C}}}\mathrm{R'}$, which then behaves analogously. N-Chloroimines prepared in other ways also give the reaction.[112]

OS **41,** 82.

C. Carbon-to-nitrogen migrations of R and Ar. These reactions have certain things in common. Reactions **8-15** to **8-18** are used to prepare amines from acid derivatives. Reactions **8-18** and **8-19** are used to prepare amines from ketones. The mechanisms of reactions **8-15, 8-16, 8-17,** and **8-18** (with carboxylic acids) are very similar and follow one of two patterns:



or



Some of the evidence[113] is: (1) configuration is retained in R (p. 783); (2) the kinetics are first order; (3) intramolecular rearrangement is shown by labeling; and (4) no rearrangement occurs *within* the migrating group, e.g., a neopentyl group on the carbon of the starting material is still a neopentyl group on the nitrogen of the product.

8-15 The Hofmann rearrangement

$$\mathrm{RCONH_2} + \mathrm{NaOBr} \longrightarrow \mathrm{R{-}N{=}C{=}O} \xrightarrow{\text{hydrolysis}} \mathrm{RNH_2}$$

In the *Hofmann rearrangement,* an unsubstituted amide is treated with sodium hypobromite (or sodium hydroxide and bromine, which is essentially the same thing) to give a primary amine which has one carbon fewer than the starting amide.[114] The actual product of the reaction is the isocyanate, but this compound is seldom isolated, since it is usually hydrolyzed under the reaction conditions. R may be alkyl or aryl, but if it is an alkyl group of more than about eight carbons, low yields are obtained unless Br_2 and NaOMe are used instead of Br_2 and NaOH. Under these conditions the product of addition to the isocyanate is the carbamate RNHCOOMe (reaction **6-18**, p. 672), which is easily isolated or may be hydrolyzed to the amine. A side reaction when NaOH is the base is formation of an acylurea RCONHCONHR by addition of $RCONH_2$ to RNCO. If this compound is desired, it may be made the main product by using only half the usual quantities of Br_2 and NaOH. Another side product, though only from primary R, is the nitrile derived from oxidation of RNH_2 (reaction **9-5**, p. 866). Imides react to give amino acids; e.g., phthalimide gives *o*-aminobenzoic acid. α-Hydroxy and α-halo amides give aldehydes and ketones by way of the unstable α-hydroxy or α-haloamines. However, a side product with an α-halo amide is a *gem*-dihalide. Ureas analogously give hydrazines. This reaction is sometimes called the *Hofmann degradation,* but this name is easily confused with reaction **7-6** (p. 758).

---

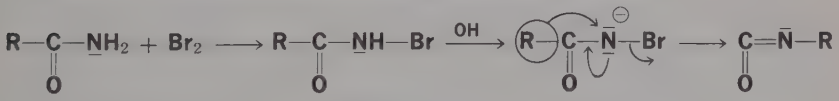
[110] Neber and Burgard, *Ann.* **493,** 281 (1932); Parcell, *Chem. Ind.* (*London*) **1963,** 1396; Ref. 109.

[111] House and Berkowitz, *J. Org. Chem.* **28,** 2271 (1963).

[112] Baumgarten, Petersen, and Wolf, *J. Org. Chem.* **28,** 2369 (1963).

[113] For a discussion of this mechanism and of the evidence for it, see Smith, in Ref. 1, vol. 1, pp. 528–550.

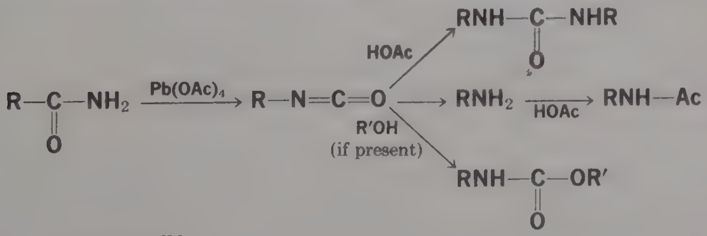
The mechanism follows the pattern outlined on page 816:



52

The first step is an example of reaction **2-36** (p. 487). In the second step, **52** loses a proton to the base. **52** is acidic because of the presence of two electron-withdrawing groups (acyl and halo) on the nitrogen. There has been controversy as to whether the third step is actually two steps: loss of bromide to form a nitrene, followed by the actual rearrangement. Most workers are now agreed that it is almost certainly concerted. N-Halo amides (**52**) have been isolated as intermediates in the reaction.

A similar reaction may be effected by the treatment of amides with lead tetraacetate.[115] In this case the initial isocyanate and the amine formed from it react with the acetic acid liberated from the lead tetraacetate to give, respectively, ureas and amides. If the reaction is carried out in the presence of an alcohol, carbamates are formed (reaction **6-18**, p. 672):



OS **II,** 19, 44, 462; **IV,** 45.

---

[114] For a review, see Wallis and Lane, *Org. Reactions* **3,** 267–306 (1946).

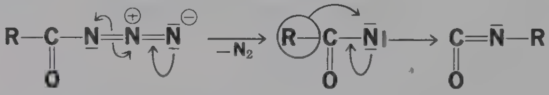
[115] Acott and Beckwith, *Chem. Commun.* **1965,** 161; Baumgarten and Staklis, *J. Am. Chem. Soc.* **87,** 1141 (1965); Acott, Beckwith, Hassanali, and Redmond, *Tetrahedron Letters* **1965,** 4039.

8-16 The Curtius rearrangement

$$\mathrm{RCON_3} \xrightarrow[\Delta]{} \mathrm{R{-}N{=}C{=}O}$$

The *Curtius rearrangement* involves the pyrolysis of acyl azides to yield isocyanates.[116] The reaction gives good yields of isocyanates, since no water is present to hydrolyze them to the amine. Of course, they may be subsequently hydrolyzed, and indeed the reaction *may* be carried out in water or alcohol, in which case the products are amines, carbamates, or acylureas, as in reaction **8-15.** This is a very general reaction and may be applied to almost any carboxylic acid: aliphatic, aromatic, alicyclic, heterocyclic, unsaturated, and containing many functional groups. Acyl azides may be prepared as in reaction **0-60** (p. 341) or by treatment of acylhydrazines (hydrazides) with nitrous acid (analogous to reaction **2-34,** p. 485). The Curtius rearrangement is catalyzed by Lewis or protic acids, but these are usually not necessary for good results.

The mechanism is similar to that in reaction **8-15:**

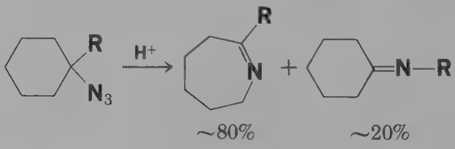


Also note the exact analogy between this reaction and reaction **8-8.** As in that case, there is no evidence for a free nitrene, and it is probable that the steps are concerted.

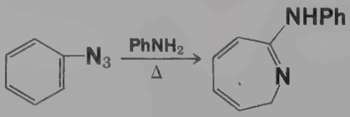
Alkyl azides may be similarly pyrolyzed to give imines, in an analogous reaction:[117]

$$\mathrm{R_3CN_3} \xrightarrow[\Delta]{} \mathrm{R_2C{=}NR}$$

The mechanism is undoubtedly the same. The R groups may be alkyl, aryl, or hydrogen, though if hydrogen migrates, the product is the unstable $\mathrm{R_2C{=}NH}$. Cycloalkyl azides give ring expansion.[118]



Aryl azides also give ring expansion on heating, e.g.,[119]



OS **III,** 846; **IV,** 819.

---

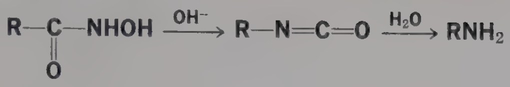
[116] For a review, see Smith, *Org. Reactions* **3,** 337–449 (1946).

[117] For a review, see Smith, Ref. 1, vol. 1, pp. 462–479.

[118] Smith and Lakritz, cited in Ref. 117, p. 474.

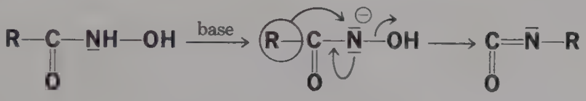
[119] Huisgen, Vossius, and Appl, *Chem. Ber.* **91,** 1, 12 (1958).

8-17 The Lossen rearrangement



$$R-\underset{\underset{O}{\|}}{C}-NHOH \xrightarrow{OH^-} R-N=C=O \xrightarrow{H_2O} RNH_2$$

Hydroxamic acids or their acyl derivatives give isocyanates when treated with bases, or sometimes even just on heating,[120] in a reaction known as the *Lossen rearrangement.* The mechanism is similar to that of reactions **8-15** and **8-16**:



This reaction is performed much less often than reactions **8-15**, **8-16**, or **8-18.** It is possible to convert ArCOOH to $ArNH_2$ in one step by heating the acid with nitromethane in polyphosphoric acid. The hydroxamic acid is an intermediate, and this is actually a Lossen rearrangement.[121]

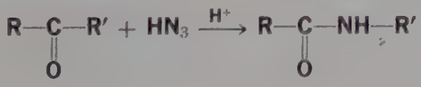
8-18 The Schmidt reaction

$$RCOOH + HN_3 \xrightarrow{H^+} R-N=C=O \xrightarrow{H_2O} RNH_2$$

There are actually three reactions called by the name *Schmidt reaction,* involving the addition of hydrazoic acid to carboxylic acids, aldehydes and ketones, and alcohols and olefins.[122] The most common is the reaction with carboxylic acids, illustrated above. Sulfuric acid is the most common catalyst, but Lewis acids have also been used. Good results are obtained for aliphatic R, especially for long chains. When R is aryl, the yields are variable, being best for sterically hindered compounds like mesitoic acid. This method has the advantage over reactions **8-15** and **8-16** that it is just one step (in practice, not in mechanism) from the acid to the amine, but conditions are more drastic.[123] Under the acid conditions employed, the isocyanate is virtually never isolated, though this has been accomplished.[124]

hydr

The reaction between a ketone and hydrazoic acid is a method for "insertion" of NH between the carbonyl group and one R group, thus converting a ketone into an amide:[125]



$$R-\underset{\underset{O}{\|}}{C}-R' + HN_3 \xrightarrow{H^+} R-\underset{\underset{O}{\|}}{C}-NH-R'$$

---

[120] For a review, see Yale, *Chem. Rev.* **33,** 209 (1943).

[121] Bachman and Goldmacher, *J. Org. Chem.* **29,** 2576 (1964).

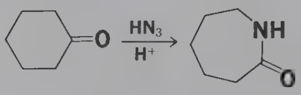
[122] For a review, see Wolff, *Org. Reactions* **3,** 307–336 (1946).

[123] For a comparison of reactions **8-15** to **8-18** as methods for converting an acid to an amine, see Ref. 116, pp. 363–366.

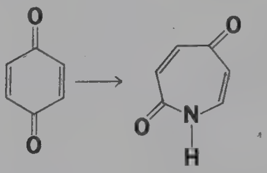
[124] Rutherford and Newman, *J. Am. Chem. Soc.* **79,** 213 (1957).

[125] For a review, see Smith, Ref. 1, vol. 1, pp. 507–527.

Either or both of the R groups may be aryl. In general, dialkyl ketones and cyclic ketones react more rapidly than alkyl aryl ketones, and these more rapidly than diaryl ketones. The latter require sulfuric acid and do not react in concentrated HCl, which is strong enough for dialkyl ketones. Dialkyl and cyclic ketones react sufficiently faster than diaryl or aryl alkyl ketones—or carboxylic acids or alcohols—that these functions may be present in the same molecule without interference. Cyclic ketones give lactams:



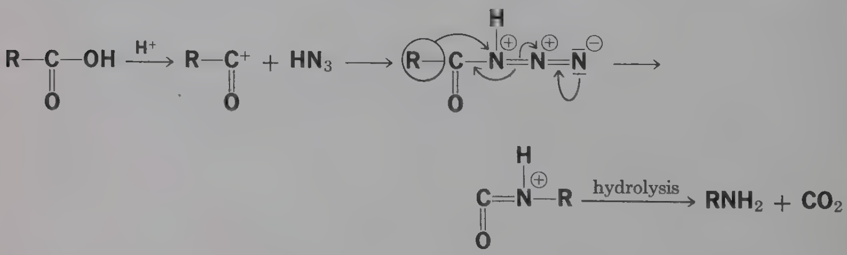
and quinones give 1*H*,2*H*,5*H*,-2,5-azepindiones:[126]



With alkyl aryl ketones, it is the aryl group that generally migrates to the nitrogen, except when the alkyl group is bulky. The reaction has been applied to a few aldehydes, but rarely. With aldehydes the product is usually the nitrile (reaction **6-23**, p. 675). Even with ketones, conversion to the nitrile is often a side reaction, especially with the type of ketone that gives reaction **7-31** (p. 776).

Alcohols and olefins react with HN_3 to give alkyl azides, which in the course of reaction rearrange in the same way as discussed in reaction **8-16.**[117]

The mechanism with carboxylic acids is similar to that of reaction **8-16,** except that it is the protonated azide which undergoes the rearrangement:



$$R-\underset{\underset{O}{\|}}{C}-OH \xrightarrow{H^+} R-\underset{\underset{O}{\|}}{C^+} + HN_3 \longrightarrow R-\underset{\underset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}^{\oplus}=N^{\oplus}=\overline{N}^{\ominus} \longrightarrow$$

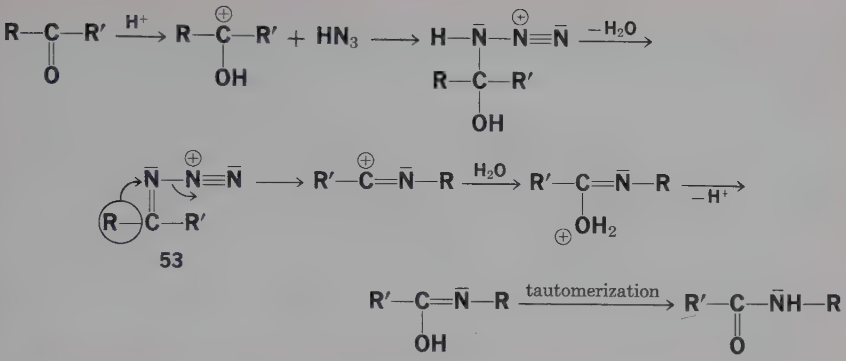
$$\underset{\underset{O}{\|}}{C}=\overset{\overset{H}{|}}{N}^{\oplus}-R \xrightarrow{\text{hydrolysis}} RNH_2 + CO_2$$

The first step is the same as that of the $A_{AC}1$ mechanism (p. 312), which explains why good results are obtained with hindered substrates. The mechanism with ketones is[127]

---

[126] Misiti, Moore, and Folkers, *Tetrahedron* **22,** 1201 (1966); Rickards and Smith, *Tetrahedron Letters* **1966,** 2361; Bedford, Jones, and Webster, *Tetrahedron Letters* **1966,** 2367.

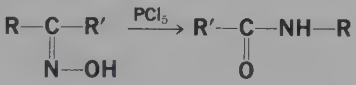
[127] Smith, *J. Am. Chem. Soc.* **70,** 320 (1948); Smith and Antoniades, *Tetrahedron* **9,** 210 (1960).



Note the similarity of this mechanism to those of "insertion" of CH_2 (reaction **8-9**) and of O (reaction **8-20**). The three reactions are essentially analogous, both in products and in mechanism. Also note the similarity of the latter part of this mechanism to that of the Beckmann rearrangement (reaction **8-19**). For evidence for this mechanism, see Reference 125, pp. 508–514.

OS **44,** 41.

8-19 The Beckmann rearrangement



$$\underset{\|\atop N-OH}{R-C-R'} \xrightarrow{PCl_5} \underset{\|\atop O}{R'-C-NH-R}$$

When oximes are treated with PCl_5, concentrated H_2SO_4, or a number of other reagents, they rearrange to substituted amides, in a reaction called the *Beckmann rearrangement.*[128] The most common reagents are concentrated H_2SO_4, PCl_5 and ether, HCl-HOAc-Ac_2O, and polyphosphoric acid.[129] The group which migrates is generally the one trans to the hydroxyl, and this is often used as a method of determining the configuration of the oxime. However, it is not unequivocal. It is known that with some oximes the cis group migrates and that with others, especially where R and R′ are both alkyl, mixtures of the two possible amides are obtained. However, this behavior does not necessarily mean that the cis group is actually undergoing the migration. In some cases it may be that the oxime undergoes isomerization under the reaction conditions *before* the migration takes place.[130] The scope of the reaction is quite broad. R and R′ may be alkyl, aryl, or hydrogen. However, hydrogen very seldom *migrates,* so that the reaction is not generally a means of converting aldoximes to unsubstituted amides $RCONH_2$. This conversion can be accomplished, though, by treatment of the aldoxime with nickel acetate under neutral conditions.[131] Not only do oximes undergo the

tran
the
hydro

---

[128] For reviews, see Donaruma and Heldt, *Org. Reactions* **11,** 1–156 (1960); Smith, in Ref. 1, vol. 1, pp. 483–507.

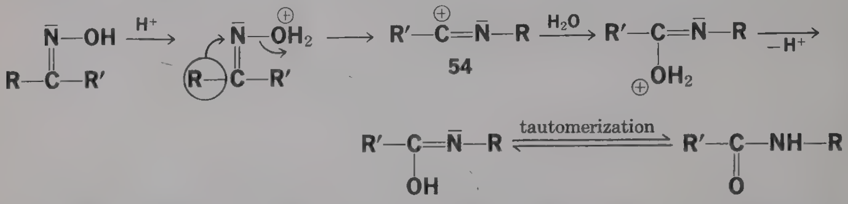
[129] For a review of Beckmann rearrangements with polyphosphoric acid, see Uhlig and Snyder, *Advan. Org. Chem.* **1,** 35–81 (1960), pp. 65–68.

[130] Lansbury and Mancuso, *Tetrahedron Letters* **1965,** 2445, have shown that some Beckmann rearrangements are *authentically* nonstereospecific.

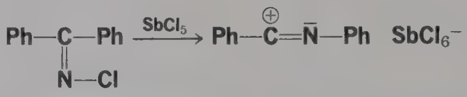
[131] Field, Hughmark, Shumaker, and Marshall, *J. Am. Chem. Soc.* **83,** 1983 (1961).

Beckmann rearrangement, but so also do esters of oximes with many acids, organic and inorganic. A side reaction with many substrates is the formation of nitriles (the "abnormal" Beckmann rearrangement, reaction **7-31**, p. 776).

In the first step of the mechanism, the OH group is converted by the reagent into a better leaving group. After that, the mechanism follows a course analogous to that for the Schmidt reaction of ketones (**8-18**) from the formation of **53** on:[132]

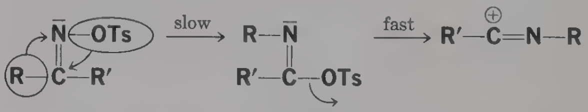


The other reagents convert OH to an ester leaving group (for example, $OPCl_4$ from PCl_5). Alternatively, the attack on **54** may be by the leaving group, if different from H_2O. An intermediate of the form **54** has been isolated by Grob and coworkers from treatment of the N-chloroimine of benzophenone:



$$\underset{\underset{\displaystyle N{-}Cl}{\|}}{Ph{-}C{-}Ph} \xrightarrow{SbCl_5} Ph{-}\overset{\oplus}{C}{=}\bar{N}{-}Ph \quad SbCl_6^-$$

and found to have a linear geometry.[133] These workers also showed that the rate of solvolysis of the oxime tosylate from cyclohexanone was about the same (actually a little greater) as that from diethyl ketone, even though the intermediate **54** from the cyclic compound cannot be linear. They thus concluded that, in this case at least, **54** cannot be formed in the rate-determining step, and that it is formed in this manner:

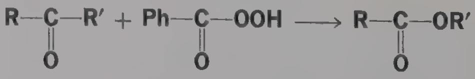


The rearrangement has also been found to take place by a different mechanism, involving formation of a nitrile by fragmentation, and then addition by a Ritter reaction (**6-54**, p. 715).[134]

OS **II,** 76, 371.

D. Carbon-to-oxygen migrations of R and Ar

8-20 The Baeyer-Villiger rearrangement



$$\underset{\underset{\displaystyle O}{\|}}{R{-}C{-}R'} + \underset{\underset{\displaystyle O}{\|}}{Ph{-}C{-}OOH} \longrightarrow \underset{\underset{\displaystyle O}{\|}}{R{-}C{-}OR'}$$

---

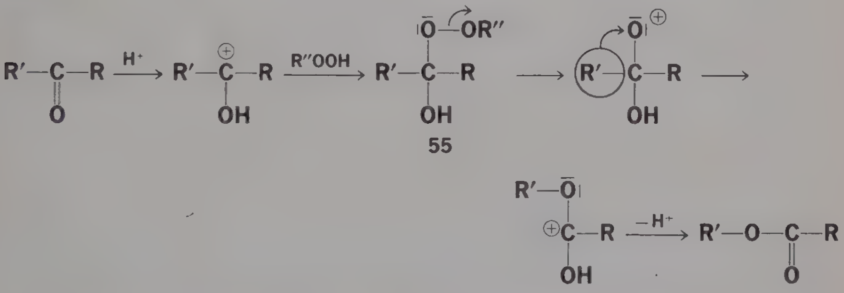
[132] For summaries of the considerable evidence for this mechanism, see Ref. 128: Donaruma and Heldt, pp. 5–14; Smith, pp. 488–493.

[133] Grob, Fischer, Raudenbusch, and Zergenyi, *Helv. Chim. Acta* **47,** 1003 (1964).

[134] Hill, Conley, and Chortyk, *J. Am. Chem. Soc.* **87,** 5646 (1965).

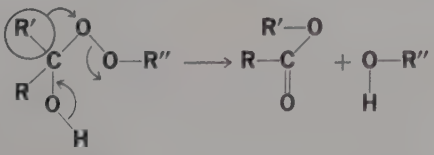
The treatment of ketones with perbenzoic acid or other peroxy compounds gives esters by "insertion" of oxygen. The reaction is called the *Baeyer-Villiger rearrangement.*[135] A particularly good oxidizing agent is peroxytrifluoroacetic acid. The reaction is often applied to cyclic ketones to give lactones. For acyclic compounds, R′ must usually be secondary, tertiary, or vinylic, although primary R′ has been rearranged with peroxytrifluoroacetic acid[136] and with BF_3-H_2O_2.[137] For unsymmetrical ketones the approximate order of migration is tertiary alkyl > secondary alkyl, aryl > primary alkyl > methyl. Diaryl ketones give the reaction but are seldom used preparatively. Enolizable β-diketones do not react. α-Diketones may be converted to anhydrides. With aldehydes, migration of hydrogen gives the carboxylic acid, and this is a way of accomplishing reaction **4-6** (p. 539). Migration of the other group would give formates, but this seldom happens, though in some cases aryl aldehydes have been converted to formates.

The mechanism[138] is similar to those of the analogous reactions with hydrazoic acid (reaction **8-18** with ketones) and with diazomethane (reaction **8-8**):



55

It is possible that loss of OR''^- and the rearrangement step are concerted. One important piece of evidence for this mechanism was that benzophenone-^{18}O gave ester which was entirely labeled in the carbonyl oxygen, with none in the alkoxyl oxygen.[139] Another view of the mechanism is that of Syrkin,[140] who suggests that **55** is converted to products by a cyclic mechanism:


55

---

[135] For reviews, see Hassall, *Org. Reactions* **9,** 73–106 (1957); Smith, in Ref. 1, vol. 1, pp. 577–589; House, "Modern Synthetic Reactions," pp. 123–129, W. A. Benjamin, Inc., New York, 1965.

[136] Emmons and Lucas, *J. Am. Chem. Soc.* **77,** 2287 (1955).

[137] McClure and Williams, *J. Org. Chem.* **27,** 24 (1962).

[138] Proposed by Criegee, *Ann.* **560,** 127 (1948).

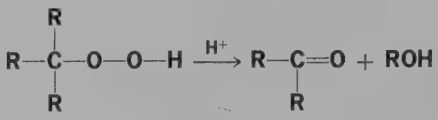
[139] Doering and Dorfman, *J. Am. Chem. Soc.* **75,** 5595 (1953). For summaries of the other evidence, see Ref. 135: Hassall, pp. 74–76; Smith, pp. 578–584.

[140] Syrkin and Moiseev, *Russ. Chem. Rev.* **29,** 193–214 (1960).

This is essentially the same as the mechanism previously shown, except that the last three steps are concerted.

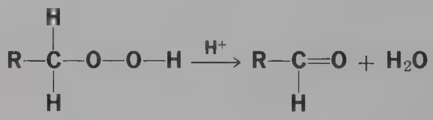
The Baeyer-Villiger rearrangement may also be accomplished with hydrogen peroxide and a base.

8-21 Rearrangement of hydroperoxides



$$\mathrm{R{-}\underset{R}{\overset{R}{C}}{-}O{-}O{-}H \xrightarrow{H^+} R{-}\underset{R}{C}{=}O + ROH}$$

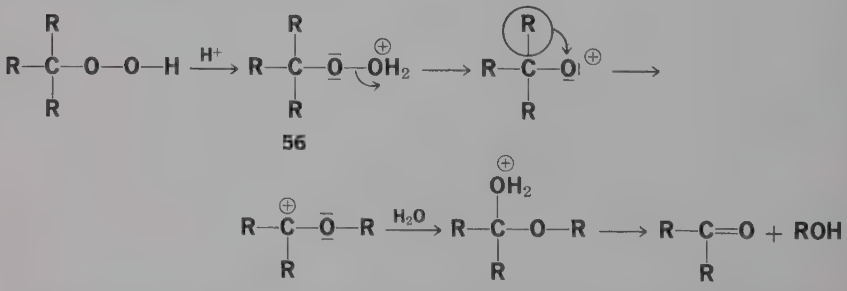
Secondary and tertiary hydroperoxides (R = alkyl or aryl) may be cleaved by proton or Lewis acids, in a reaction whose principal step is a rearrangement. The reaction has also been applied to peroxy esters $R_3COOCOR'$, but less often. When aryl and alkyl groups are both present, migration of aryl dominates. With primary hydroperoxides it is the hydrogen that migrates, so that the product is an aldehyde:



$$\mathrm{R{-}\underset{H}{\overset{H}{C}}{-}O{-}O{-}H \xrightarrow{H^+} R{-}\underset{H}{C}{=}O + H_2O}$$

The same thing occurs with secondary peroxides when the two R groups are both alkyl. It is not necessary actually to prepare and isolate hydroperoxides. The reaction takes place when the alcohols are treated with H_2O_2 and acids.

The mechanism is as follows:



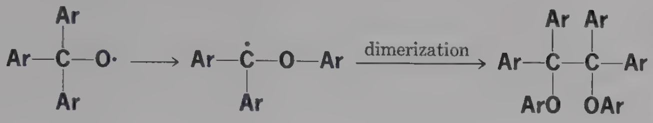
56

The last step is hydrolysis of the unstable hemiacetal. Once again, the loss of water from **56** and the actual migration may be concerted. Hydroperoxides may also rearrange in a different way: $Ar_3COOH + Fe^{++} \longrightarrow \underset{ArO}{Ar_2C}{-}\underset{OAr}{CAr_2}$.[141]

---

[141] Wieland, *Ber.* **44**, 2553 (1911).

This has a free-radical mechanism:[142]

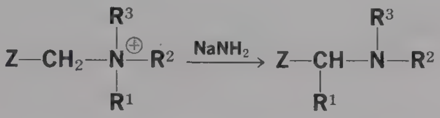


$$\mathrm{Ar_3C{-}O\cdot \longrightarrow Ar_2\dot{C}{-}O{-}Ar \xrightarrow{\text{dimerization}} Ar_2C(OAr){-}C(OAr)Ar_2}$$

OS **40**, 76.

E. Nitrogen-to-carbon and oxygen-to-carbon migration

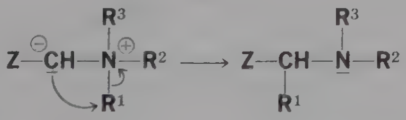
8-22 The Stevens rearrangement



$$\mathrm{Z{-}CH_2{-}\overset{\oplus}{N}R^1R^2R^3 \xrightarrow{NaNH_2} Z{-}CH(R^1){-}NR^2R^3}$$

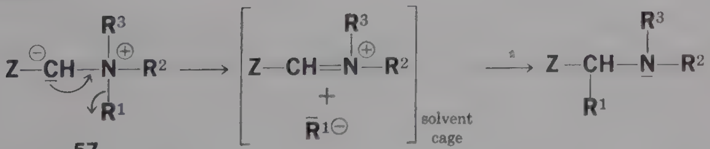
In the *Stevens rearrangement* a quaternary ammonium salt containing an electron-withdrawing group Z on one of the carbons attached to the nitrogen is treated with a strong base (such as $NaNH_2$) to give a rearranged tertiary amine. Z is a group such as RCO, ROOC, phenyl, etc.[143] The most common migrating groups are allyl, benzhydryl, 9-fluorenyl, 3-phenylpropargyl, and phenacyl, though even methyl migrates to a sufficiently negative center. That the mechanism is intramolecular was shown by crossover experiments and by ^{14}C labeling.[144] The first step of the reaction is removal of the acidic proton to give an ylide (**57**), which could then rearrange in two possible ways: with the migrating group either carrying the electrons or leaving them behind:

Mechanism *a*



57

Mechanism *b*



57

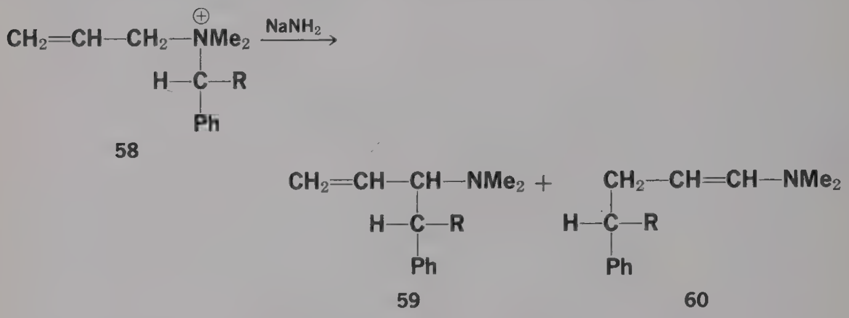
---

[142] Kharasch, Poshkus, Fono, and Nudenberg, *J. Org. Chem.* **16**, 1458 (1951).

[143] For reviews of the Stevens rearrangement, and of the closely related Wittig rearrangement (reaction **8-23**), see Zimmerman, in Ref. 1, vol. 1, pp. 345–406; and Cram, "Fundamentals of Carbanion Chemistry," pp. 223–233, Academic Press Inc., New York, 1965.

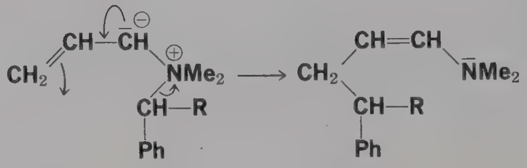
[144] Stevens, *J. Chem. Soc.* **1930**, 2107; Johnstone and Stevens, *J. Chem. Soc.* **1955**, 4487.

Mechanism *a* is similar to the carbanion mechanism of reaction **8-1.** Retention of configuration is found at R^1,[145] and this would therefore be an S_Ni mechanism with respect to the migrating group. However, doubt has been cast on this mechanism by the following result: optically active **58** rearranged to **59** (with the benzyl and not the allyl migrating) and **60** (by a 1,4-shift). The benzyl group retained its configuration in **59**, as expected, but also in **60.**[146] If the benzyl group were migrating without its electrons (mechanism *a*), then it would have to move over this long distance either as a relatively free carbonium ion (and be racemized) or in an S_Ni' process (p. 272) (and be inverted):

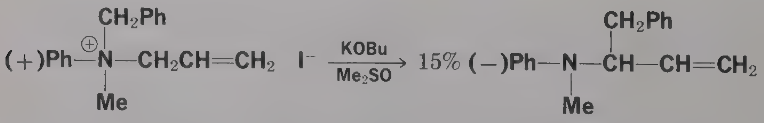


$$CH_2{=}CH{-}CH_2{-}\overset{\oplus}{N}Me_2(CHRPh) \xrightarrow{NaNH_2} CH_2{=}CH{-}CH(CHRPh){-}NMe_2 + CH_2(CHRPh){-}CH{=}CH{-}NMe_2$$

58 **59** **60**



In neither case would there be retention. Therefore, the 1,4-shift appears to operate by mechanism *b*. If the 1,4-shift operates by mechanism *b*, it is unlikely that the 1,2-shift has a different mechanism. In mechanism *b* the two ions do not drift apart because they are held together in a solvent cage. An interesting finding which is compatible with both mechanisms is that optically active allylbenzylmethylphenylammonium iodide (asymmetric nitrogen, see p. 75) gave optically active product:[147]



$$(+)Ph{-}\overset{\oplus}{N}(CH_2Ph)(Me){-}CH_2CH{=}CH_2\ I^- \xrightarrow[Me_2SO]{KOBu} 15\%\ (-)Ph{-}N(Me){-}CH(CH_2Ph){-}CH{=}CH_2$$

The Sommelet-Hauser rearrangement competes when Z is an aryl group (see reaction **3-27**, p. 516).

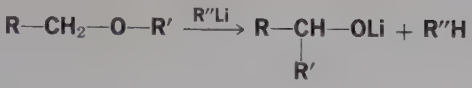
---

[145] Brewster and Kline, *J. Am. Chem. Soc.* **74**, 5179 (1952).

[146] Jenny and Druey, *Angew. Chem. Intern. Ed. Engl.* **1**, 155 (1962).

[147] Hill and Chan, *J. Am. Chem. Soc.* **88**, 866 (1966).

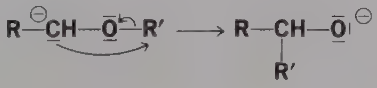
8-23 The Wittig rearrangement



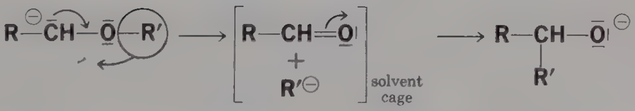
$$R{-}CH_2{-}O{-}R' \xrightarrow{R''Li} R{-}\underset{\displaystyle R'}{\underset{|}{CH}}{-}OLi + R''H$$

The rearrangement of ethers with alkyllithiums is called the *Wittig rearrangement* (not to be confused with the Wittig reaction, **6-45**, p. 702) and is similar to reaction **8-22**.[143] However, a stronger base is required (e.g., phenyllithium or sodium amide). R and R′ may be alkyl or aryl. Also, one of the hydrogens may be alkyl or aryl, in which case the product is the salt of a tertiary alcohol. Migratory aptitudes here are allyl, benzyl > methyl, ethyl > phenyl.[148] Here too, two mechanisms may be envisioned, parallel to mechanisms *a* and *b* of reaction **8-22**, after removal of the proton:

Mechanism *a*

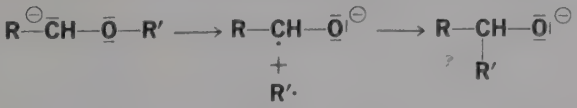


Mechanism *b*



However, mechanism *b* differs from that in reaction **8-22** in that in that case both fragments are charged. The migratory order is evidence for mechanism *a*, since this is the order of carbonium-ion stability. On the other hand, there are a number of facts in agreement with mechanism *b*: (1) aldehydes are obtained as side products;[149] (2) partial racemization of R′ has been observed;[150] and (3) crossover products have been detected, which could not happen with mechanism *a*.[151] It is possible that the two mechanisms operate in different cases.[152]

Still a third possible mechanism has been proposed which is similar to mechanism *b* except that the cleavage gives a pair of radicals:[153]



---

[148] Wittig, *Angew. Chem.* **66,** 10 (1954).

[149] For example, see Hauser and Kantor, *J. Am. Chem. Soc.* **73,** 1437 (1951); Cast, Stevens, and Holmes, *J. Chem. Soc.* **1960,** 3521.

[150] Schöllkopf and Fabian, *Ann.* **642,** 1 (1961); Schöllkopf and Schaffer, *Ann.* **663,** 22 (1963).

[151] Lansbury and Pattison, *J. Org. Chem.* **27,** 1933 (1962); *J. Am. Chem. Soc.* **84,** 4295 (1962).

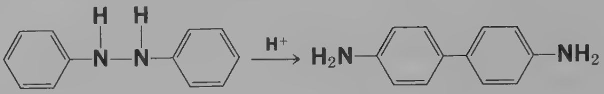
[152] Ref. 151; Schöllkopf and Walter, *Ann.* **654,** 27 (1962); and references cited in these papers.

[153] Lansbury, Pattison, Sidler, and Bieber, *J. Am. Chem. Soc.* **88,** 78 (1966).

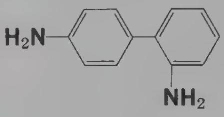
Non-1,2-rearrangements

A. Cyclic rearrangements

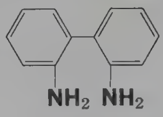
8-24 The benzidine rearrangement



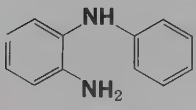
When hydrazobenzene is treated with acids, it rearranges to give about 70% 4,4′-diaminobiphenyl (benzidine) and about 30% 2,4′-diaminobiphenyl (**61**). This reaction is called the *benzidine rearrangement* and is general for N,N′-diarylhydrazines.[154] Usually the major product is the 4,4′-diaminobiaryl, but four other products may also be produced. These are the 2,4′-diaminobiaryl (**61**), already referred to, the 2,2′-diaminobiaryl (**62**), and



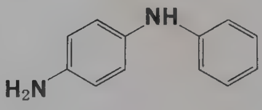
61



62



63



64

the *o*- and *p*-arylaminoanilines (**63** and **64**), called *semidines*. The 2,2′-diaminobiaryl and the *p*-semidine are formed less often and in smaller amounts than the other two side products. Usually the 4,4′-diaminobiaryl predominates except when one or both of the para positions of the diarylhydrazine are occupied. However, the 4,4′-diamine may still be produced even if the para positions are occupied. If SO_3H, COOH, or Cl (but not R, Ar, or NR_2) is present in the para position, it may be ejected. With dinaphthylhydrazines, the major products are not the 4,4′-diaminobinaphthyls, but the 2,2′-isomers. Another side reaction is disproportionation to $ArNH_2$ and ArN=NAr. For example, *p,p*′-$PhC_6H_4NHNHC_6H_4Ph$ gives no rearrangement products, only disproportionation.

The mechanism has been exhaustively studied, and several mechanisms have been proposed.[155] At one time it was believed that NHAr broke away from ArNHNHAr and then became attached to the para position to give the semidine (**64**), which then went on to product. The fact that semidines could be isolated lent this argument support, as did the fact that this would be analogous to the rearrangements considered in Chapter 11 (reactions **1-33** to **1-37**). However, this theory was killed when it was discovered that semidines could not be converted to benzidines under the reaction conditions.

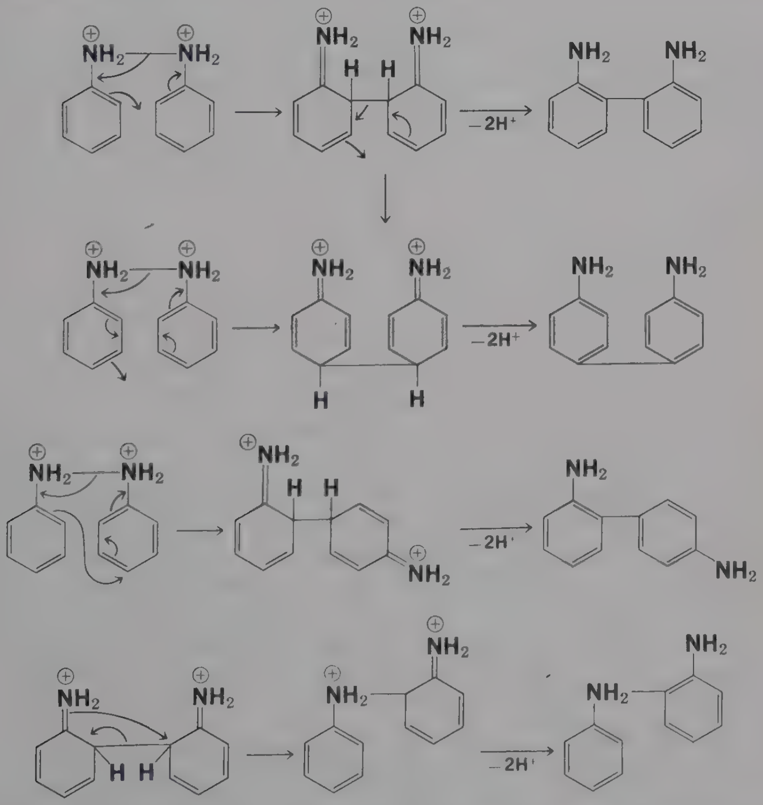
---

[154] For a review, see Hughes and Ingold, *Quart. Rev.* (*London*) **6**, 34–62 (1956).

[155] For discussions, see Dewar, in Ref. 1, vol. 1, pp. 295–344, 323–344; Banthorpe, Hughes, and Ingold, *J. Chem. Soc.* **1964**, 2864–2900. Each of these papers strongly argues in favor of one mechanism (a different one in each case).

Cleavage into two independent pieces (either ions or free radicals) has been ruled out by many types of crossover experiment, which always show that the two rings of the starting material are in the product; that is, ArNHNHAr′ gives no molecules (of any of the five products) containing two Ar groups or two Ar′ groups, and mixtures of ArNHNHAr and Ar′NHNHAr′ give no molecules containing both Ar and Ar′. An important piece of evidence was the discovery that the reaction is often *second order* in H^+, so that two molecules of H^+ are involved in the rate-determining step.[156] This would seem to indicate that the actual reacting species is the diprotonated substrate, $\mathrm{Ar{-}\overset{\oplus}{N}H_2{-}\overset{\oplus}{N}H_2{-}Ar}$.

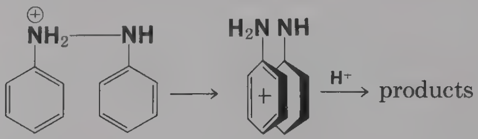
One mechanism, called the "polar-transition-state" mechanism, was proposed by Banthorpe, Hughes, and Ingold.[155] This mechanism has the electrons moving around a ring, with the rings linking up in the 2,2′, 4,4′, or 2,4′ manner. These intermediates can go to product, or they can convert from one to another (shown for the 2,2′ ⟶ the 4,4′), or they can go to semidine (shown for 2,2′ ⟶ the *o*-semidine):



According to this mechanism the N—N bond is broken because of the repulsion between two positive nitrogens. Another mechanism, called the π-complex mechanism, was proposed by Dewar;[155] it envisions a cleavage of the monoprotonated substrate into two parts which are held together by a π-orbital overlap between a filled orbital of the benzene-type ring and an empty orbital of the other.

---

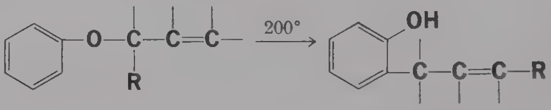
[156] Hammond and Shine, *J. Am. Chem. Soc.* **72**, 220 (1950).



Since the rings are held together at the centers, it is easy to see how they can rotate to form the various products. In this view the role of the second proton is to attack the complex in the rate-determining step. More recently it has been proposed[157] that the role of the hydrogen ion is to hold the rings together by getting in between them. According to this viewpoint, there is a sandwich in which the proton is hydrogen-bonded to the π electrons of each ring. The second proton protonates a nitrogen. Complicating matters further was the discovery that many benzidine rearrangements are first order in hydrogen[158] and that the reaction may even proceed without any acid at all, merely on heating.[159] Fractional rate orders have also been observed,[160] but it has been shown that these are the result of simultaneous first-order and second-order (in H^+) processes.

Despite the immense amount of work done on this unique reaction, it seems that much more needs to be done before a mechanism is established with which all can agree.[161]

8-25 The Claisen rearrangement



Allyl aryl ethers, when heated, rearrange to *o*-allylphenols in a reaction called the *Claisen rearrangement.*[162] If both ortho positions are filled, the allyl group migrates to the para position (this is often called the *para-Claisen rearrangement*). Sometimes some para product is obtained even if one or both ortho positions are free,[163] although in general it may be said that, when one or both ortho positions are open, the product is the *ortho*-allylphenol and that, when both ortho positions are blocked, the product is the para compound. There is no reaction when the para and both ortho positions are filled. Migration to the meta position has not been observed.

---

[157] Ferstandig, *Tetrahedron Letters* **1963**, 1235.

[158] Banthorpe, Hughes, and Ingold, *J. Chem. Soc.* **1962**, 2386, 2402, 2407, 2413, 2418, 2429; Shine and Chamness, *J. Org. Chem.* **28**, 1232 (1963); and references cited in these papers.

[159] Shine and Trisler, *J. Am. Chem. Soc.* **82**, 4054 (1960); Banthorpe and Hughes, *J. Chem. Soc.* **1964**, 2849, 2860; Banthorpe, *J. Chem. Soc.* **1964**, 2854.

[160] Carlin and Odioso, *J. Am. Chem. Soc.* **76**, 100 (1954).

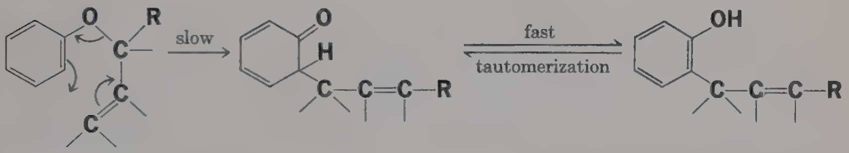
[161] See the discussion by Ingold in "The Transition State," *Chem. Soc.* (*London*) *Spec. Publ.* **16**, pp. 118–138, 1962.

[162] For reviews, see Tarbell, *Org. Reactions* **2**, 1–48 (1944); Rhoads, in Ref. 1, vol. 1, pp. 660–684.

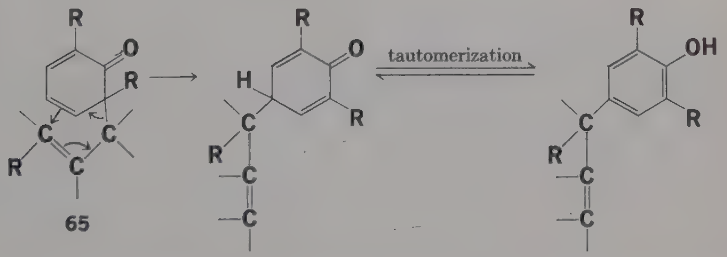
[163] Borgulya, Hansen, Barner, and Schmid, *Helv. Chim. Acta* **46**, 2444 (1963).

In the ortho migration the allyl group always undergoes an allylic shift. That is, as shown above, a substituent α to the oxygen is now γ to the ring (and vice versa). On the other hand, in the para migration there is never an allylic shift: the allyl group is found exactly as it was in the original ether. Propargyl groups (that is, groups with a triple bond in the appropriate position) do not generally rearrange.

The mechanism is cyclic and accounts for all of these facts. For the ortho rearrangement:



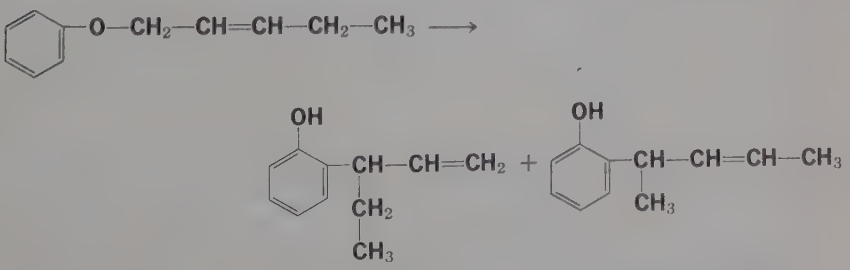
Evidence is the lack of a catalyst, the fact that the reaction is first order in the ether, the absence of crossover products when mixtures are heated, and the presence of the allylic shift, which is required by this mechanism. The allylic shift for the ortho rearrangement (and the absence of one for the para) has been demonstrated by ^{14}C labeling even when no substituents are present. When the ortho positions have no hydrogen, a second migration follows:



65

and the group is restored to its original structure. Intermediates of structure **65** have been trapped by means of a Diels-Alder reaction.[164]

Ethers with an alkyl group in the γ position ($ArO{-}C{-}C{=}C{-}R$ systems) sometimes give abnormal products, with the β-carbon becoming attached to the ring:

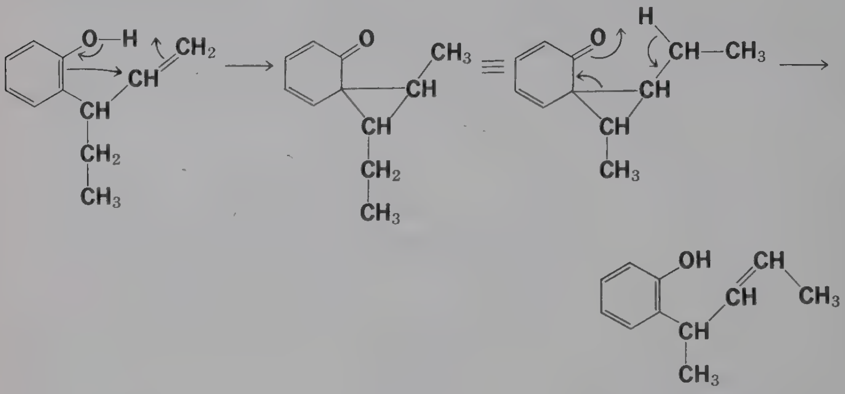


Normal product Abnormal product

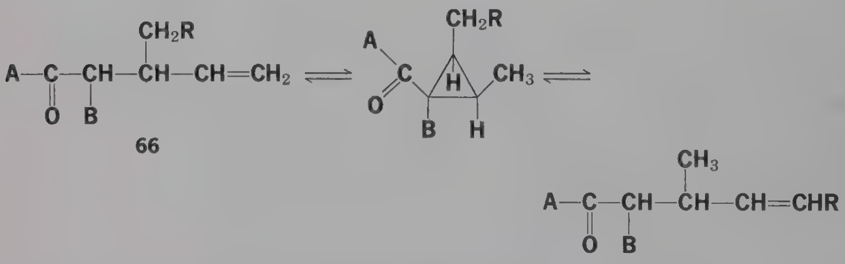
---

[164] Conroy and Firestone, *J. Am. Chem. Soc.* **75**, 2530 (1953).

It has been established that these abnormal products do not arise directly from the starting ether but are formed by a further rearrangement of the normal product:[165]



This is an interesting rearrangement, in which a shift of three electron pairs takes place over *seven* atoms. It has been found that this "abnormal" Claisen reaction is general and can interconvert systems of types **66** and **67** through a cyclopropane ring:[166]



66

67

A = H, R, Ar, OR, etc.
B = H, R, Ar, COR, COAr, COOR, etc.

Since the Claisen rearrangement mechanism does not involve ions, it should not be greatly dependent on the presence or absence of substituent groups on the ring. This is the case. Electron-donating groups increase the rate, and electron-withdrawing groups decrease it, but the effect is small, with the *p*-amino compound reacting only about ten to twenty times faster than the *p*-nitro compound.[167] Most Claisen rearrangements are performed without a catalyst, but $AlCl_3$ is sometimes used. In this case it becomes a Friedel-Crafts reaction, the mechanism is no longer cyclic, and ortho, meta, and para products may be obtained.

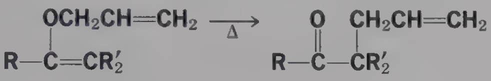
---

[165] Marvell, Anderson, and Ong, *J. Org. Chem.* **27**, 1109 (1962); Habich, Barner, Roberts, and Schmid, *Helv. Chim. Acta* **45**, 1943 (1962); Lauer and Johnson, *J. Org. Chem.* **28**, 2913 (1963); Habich, Barner, Philipsborn, and Schmid, *Helv. Chim. Acta* **48**, 1297 (1965).

[166] Roberts and Landolt, *J. Am. Chem. Soc.* **87**, 2281 (1965); Roberts, Greene, Landolt, and Heyer, *J. Am. Chem. Soc.* **87**, 2282 (1965).

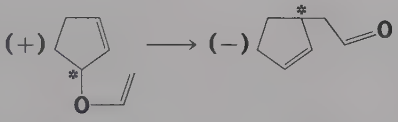
[167] Goering and Jacobson, *J. Am. Chem. Soc.* **80**, 3277 (1958); White, Gwynn, Schlitt, Girard, and Fife, *J. Am. Chem. Soc.* **80**, 3271 (1958); White and Fife, *J. Am. Chem. Soc.* **83**, 3846 (1961); White, Slater, and Fife, *J. Org. Chem.* **26**, 627 (1961); White and Slater, *J. Org. Chem.* **27**, 2908 (1962).

Allyl ethers of enols (allyl vinyl ethers) also give the Claisen rearrangement; in fact it was discovered with these compounds first:[168]



$$R{-}\overset{\displaystyle OCH_2CH{=}CH_2}{\overset{|}{C}}{=}CR'_2 \xrightarrow[\Delta]{} R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}\overset{\displaystyle CH_2CH{=}CH_2}{\overset{|}{C}}R'_2$$

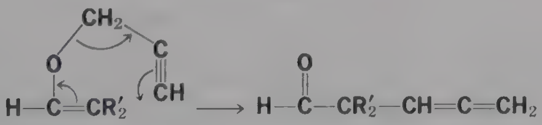
In these cases, of course, the final tautomerization does not take place even when R′ = H, since there is no aromaticity to restore, and ketones are more stable than enols. The mechanism is similar to that with allyl aryl ethers. One experiment which demonstrated this was the conversion of optically active **68** to **69** which was still optically active.[169] This is another example of asymmetric induction (p. 91):



68 **69**

It is possible to treat ketones with allyl alcohol and an acid catalyst to give γ,δ-unsaturated ketones directly, presumably by initial formation of the vinyl ethers, and then Claisen rearrangement.[170]

A number of expected analogs of the Claisen rearrangement are known, e.g., rearrangement of $ArNHCH_2CH{=}CH_2$[171] and of $RC(OCH_2CH{=}CH_2){=}NR$. Propargyl vinyl ethers give allenic aldehydes:[172]



Under strenuous conditions (potassium *tert*-butoxide in *tert*-butyl alcohol at 350° for 24 hr) the reaction has even been extended to a carbon analog: a mixture of 1-phenylbutenes was placed in equilibrium with a mixture of 1-(*o*-tolyl)propenes.[173] However, allyl aryl thioethers $ArSCH_2CH{=}CH_2$ do not give *ortho*-allyl thiophenols but yield bicyclic compounds instead.[174]

---

[168] Claisen, *Ber.* **45,** 3157 (1912).

[169] Hill and Edwards, *Tetrahedron Letters* **1964,** 3239.

[170] Lorette, *J. Org. Chem.* **26,** 4855 (1961).

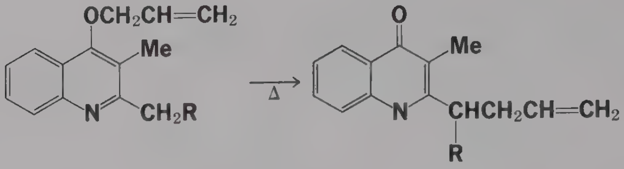
[171] Marcinkiewicz, Green, and Mamalis, *Tetrahedron* **14,** 208 (1961).

[172] Black and Landor, *J. Chem. Soc.* **1965,** 6784.

[173] Doering and Bragole, *Tetrahedron* **22,** 385 (1966).

[174] Kwart and Hackett, *J. Am. Chem. Soc.* **84,** 1754 (1962); Kwart and Evans, *J. Org. Chem.* **31,** 413 (1966); Meyers, Rinaldi, and Banoli, *J. Org. Chem.* **28,** 2440 (1963); Makisumi, *Tetrahedron Letters* **1966,** 6399.

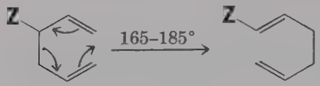
In some cases rearrangement has been shown to go to the α position of a meta side chain:[175]



The mechanism of this process is the same as that of the para-Claisen rearrangement.

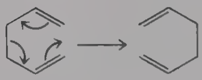
OS **III,** 418; **42,** 14.

8-26 The Cope rearrangement and related reactions

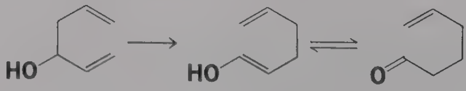


$Z =$ **Ph, RCO,** etc.

When 1,5-dienes are heated, they isomerize, in a reaction known as the *Cope rearrangement* (not to be confused with the Cope elimination reaction, **7-8,** p. 761).[176] When the diene is symmetrical about the 3,4-bond, we have the unusual situation where a reaction gives a product which is identical with the starting material:



Therefore, a Cope rearrangement can be detected only when the diene is not symmetrical about this bond. Any 1,5-diene gives the rearrangement; for example, 3-methyl-1,5-hexadiene heated to 300° gives 1,5-heptadiene.[177] However, the reaction takes place more easily (lower temperature required) when there is a group on the 3- or 4-carbon with which the new double bond may conjugate. The reaction is obviously reversible and produces an equilibrium mixture of the two 1,5-dienes which is richer in the thermodynamically more stable isomer. However, the reaction cannot be reversed for 3-hydroxy-1,5-dienes, because the product tautomerizes to the ketone or aldehyde:



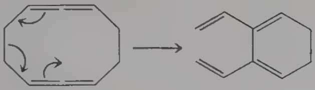
---

[175] Makisumi, *J. Org. Chem.* **30,** 1989 (1965).

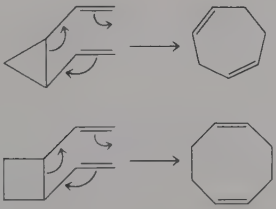
[176] For reviews, see Vogel, *Angew. Chem. Intern. Ed. Engl.* **2,** 1–11 (1963); Doering and Roth, *Angew. Chem. Intern. Ed. Engl.* **2,** 115–122 (1963); Rhoads, in Ref. 1, vol. 1, pp. 684–706.

[177] Levy and Cope, *J. Am. Chem. Soc.* **66,** 1684 (1944).

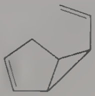
This has been called the *oxy-Cope rearrangement.*[178] The 1,5-diene system may be inside a ring, or it may be part of an allenic system (this example illustrates both of these situations):[179]



but the reaction does not take place when one of the double bonds is part of an aromatic system, e.g., 4-phenyl-1-butene. When the two double bonds are in vinyl groups attached to adjacent ring positions, then the product is a ring which is four carbons larger. This has been applied to divinylcyclopropanes and cyclobutanes:[180]

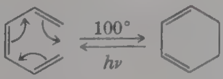


Indeed *cis*-1,2-divinylcyclopropanes give this rearrangement so rapidly that they generally cannot be isolated, though an exception is *cis*-6-vinylbicyclo[3.1.0]hex-2-ene (**70**), which has a half-life of 1 day at 25°.[181]



70

A special case of a 1,5-diene is a conjugated triene, and these compounds also undergo the rearrangement, but in this case the 3,4-bond goes from a double to a single rather than from a single to no bond, so that the product always has one more ring than the triene. The isomer with the extra ring is usually the more stable. Examples are



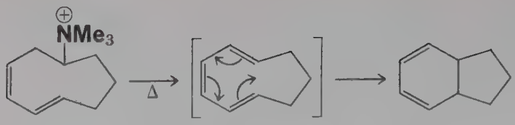
---

[178] Berson and Jones, *J. Am. Chem. Soc.* **86**, 5017, 5019 (1964); Viola and Levasseur, *J. Am. Chem. Soc.* **87**, 1150 (1965).

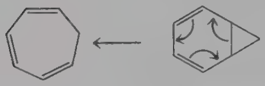
[179] Harris, *Tetrahedron Letters* **1965**, 1359.

[180] Vogel, Ott, and Gajek, *Ann.* **644**, 172 (1961).

[181] Brown, *Chem. Commun.* **1965**, 226.

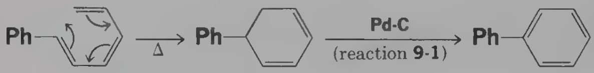


Not isolated

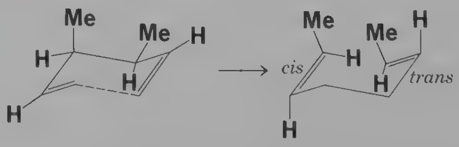


Norcaradiene

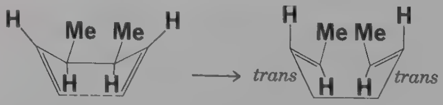
In the latter case, because of the strain (and because it is a *cis*-1,2-divinylcyclopropane), the compound with two rings is less stable than the cycloheptatriene, and norcaradienes cannot generally be isolated. Biphenyls may be prepared by pyrolysis of phenyltrienes, and subsequent aromatization:[182]



As we have indicated with our arrows, the mechanism of the Cope rearrangement is a simple six-centered process, similar to that of reaction **8-25.** The evidence is similar to that for reaction **8-25.** Since the mechanism is so simple, it has been possible to study some rather subtle points, among them the question of whether the six-membered transition state is in the boat or the chair form.[183] For the case of 3,4-dimethyl-1,5-hexadiene it was demonstrated conclusively that the transition state is in the chair form. This was shown by the stereospecific nature of the reaction: the meso isomer gave the cis-trans product, while the DL compound gave the trans-trans diene.[184] Now if the transition state is in the chair form (taking the meso isomer, for example), one methyl must be "axial" and the other "equatorial," and the product must be the cis-trans olefin:



There are two possible boat forms for the transition state of the meso isomer. One of these will lead to a trans-trans product:



---

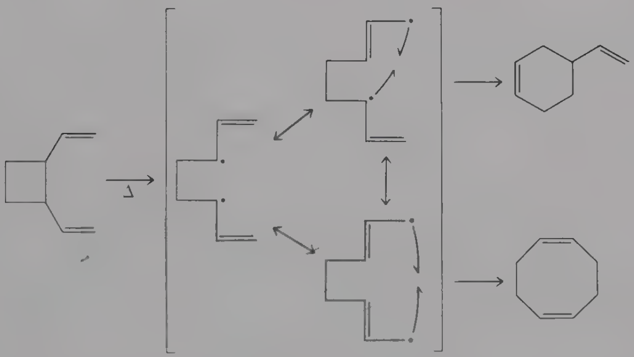
[182] Edmunds and Johnstone, *J. Chem. Soc.* **1965,** 2898.

[183] This question has been studied for the Claisen rearrangement also. See Rhoads, Ref. 1, vol. 1, pp. 694–696.

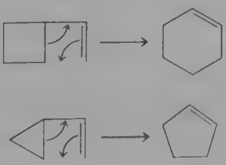
[184] Doering and Roth, *Tetrahedron* **18,** 67 (1962).

and the other to a cis-cis olefin. For the DL pair the predictions are just the opposite: there is just one boat form, and it leads to the cis-trans olefin, while one chair form ("diaxial" methyls) leads to the cis-cis product and the other ("diequatorial" methyls) predicts the trans-trans product. Thus the nature of the products obtained demonstrates that the transition state is a chair and not a boat.[185] However, 3,4-dimethyl-1,5-hexadiene is free to assume either the chair or boat (it prefers the chair), but other compounds are not so free. Thus 1,2-divinylcyclopropane (p. 835) can react *only* in the boat form, demonstrating that such reactions are not impossible.

Not all Cope rearrangements proceed by the cyclic six-centered mechanism. Thus *cis*-1,2-divinylcyclobutane (p. 835) rearranges smoothly to 1,5-cyclooctadiene, since the geometry is favorable. The trans isomer also gives this product, but the main product is 4-vinylcyclohexene. This reaction proceeds by a diradical mechanism.[186]



There are certain reactions, closely related to the Cope rearrangement, which do not involve 1,5-dienes. One such reaction is ring expansion of a vinylcycloalkane, e.g.,[187]



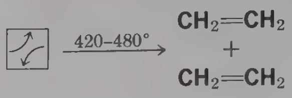
This has been applied only to small rings, so that ring strain is undoubtedly a factor in such ring expansions. The transition state is four-membered. A similar transition state is involved in the cleavage of cyclobutanes:[188]

---

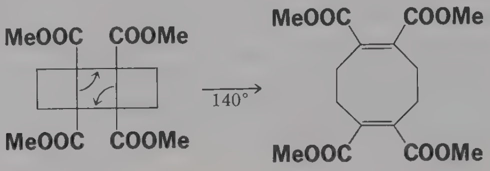
[185] Preference for the chair transition state is a consequence of orbital symmetry relationships (see pp. 633 and 839): Hoffmann and Woodward, *J. Am. Chem. Soc.* **87**, 4389 (1965); Fukui and Fujimoto, *Tetrahedron Letters* **1966**, 251.

[186] Hammond and De Boer, *J. Am. Chem. Soc.* **86**, 899 (1964); Trecker and Henry, *J. Am. Chem. Soc.* **86**, 902 (1964); also see Gibson and Pettit, *J. Am. Chem. Soc.* **87**, 2620 (1965).

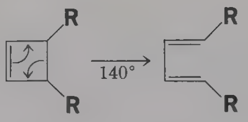
[187] Overberger and Borchert, *J. Am. Chem. Soc.* **82**, 1007 (1960).



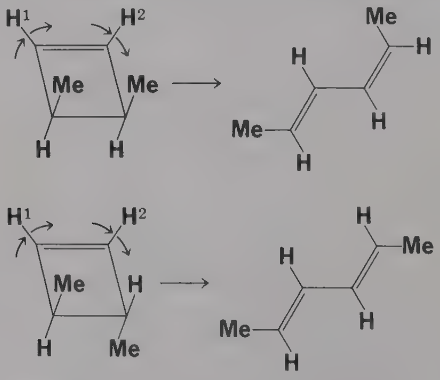
This, of course, is not a rearrangement but a fission. However, the same reaction is a rearrangement when the cyclobutane is incorporated into a larger ring system, e.g.,[189]



For *cyclobutenes* the same reaction is always a rearrangement, even when the ring stands alone:[190]



Cyclobutenes may thus be converted to 1,3-dienes. The reaction is generally not reversible (except photochemically), but one butadiene (*cis,trans*-1,3-cyclooctadiene) has been thermally converted to a cyclobutene.[191] The stereochemistry of the butadiene-cyclobutene conversion has been investigated. It was found that *cis*-3,4-dimethylcyclobutene gave only *cis,trans*-2,4-hexadiene, while the trans isomer gave only the trans-trans diene:[192]



---

[188] Genaux, Kern, and Walters, *J. Am. Chem. Soc.* **75**, 6196 (1953).

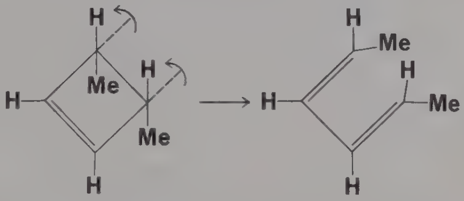
[189] Vogel, *Angew. Chem.* **72**, 4 (1960).

[190] Vogel, *Angew. Chem.* **66**, 640 (1954); *Ann.* **615**, 1 (1958).

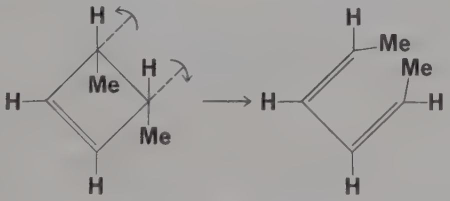
[191] Shumate, Neuman, and Fonken, *J. Am. Chem. Soc.* **87**, 3996 (1965). See also Gil-Av and Herling, *Tetrahedron Letters* **1967**, 1.

[192] Winter, *Tetrahedron Letters* **1965**, 1207. Also see Vogel, *Ann.* **615**, 14 (1958); Criegee and Noll, *Ann.* **627**, 1 (1959).

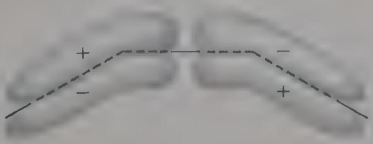
This is evidence for the four-centered cyclic transition state and arises from *conrotatory* motion of the C-1 and C-2 hydrogens. That is, as H^1 moves up, H^2 moves down. It is called conrotatory because they are both moving clockwise (or both counterclockwise). The other possibility (*disrotatory* motion) would have one moving clockwise while the other moves counterclockwise. Another way to look at this is to observe the motions of the methyl groups and of the C-3 and C-4 hydrogens. In conrotatory motion they rotate in the same direction (and the cis isomer gives the cis-trans diene):[193]



On the other hand, in a disrotatory motion, in which they moved in opposite ways, the cis isomer would have given the cis-cis diene (shown), or the trans-trans diene:



If the motion had been disrotatory, this would still have been evidence for a cyclic mechanism. If the mechanism were a diradical or some other kind of noncyclic process, it is likely that no stereospecificity of either kind would have been observed. In contrast, the thermal cyclization of hexatrienes is disrotatory, while the photochemical cyclization is conrotatory. These conrotatory and disrotatory motions are a consequence of the symmetry rules mentioned in Chapter 15 (p. 633).[194] As applied to the conversion of cyclobutenes to butadienes, the principle of conservation of orbital symmetry may be expressed: a σ bond will open in such a way that the resulting p orbitals will have the symmetry of the highest-occupied π orbital of the product. In the case of cyclobutenes, the highest-occupied orbital of the product (1,3-butadienes) has the symmetry.

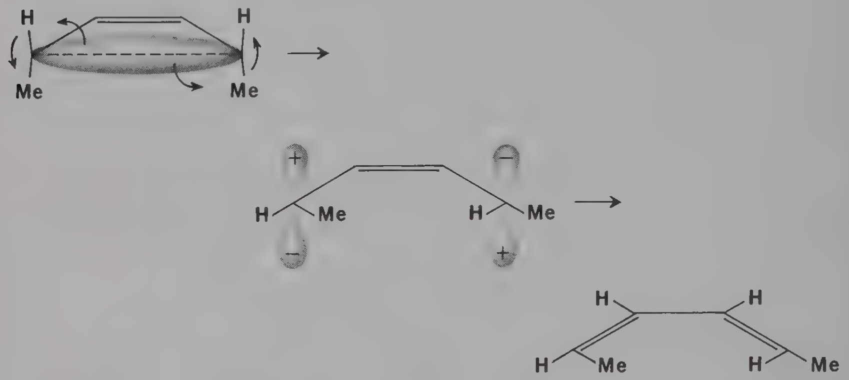


---

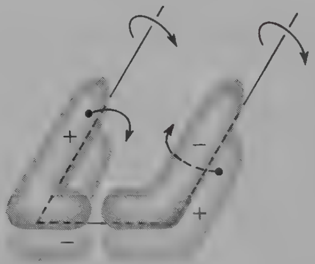
[193] This picture is from Woodward and Hoffmann, *J. Am. Chem. Soc.* **87**, 395 (1965), who coined the terms conrotatory and disrotatory.

[194] Woodward and Hoffmann, *J. Am. Chem. Soc.* **87**, 395 (1965). Also see Longuet-Higgins and Abrahamson, *J. Am. Chem. Soc.* **87**, 2045 (1965); Fukui, *Tetrahedron Letters* **1965**, 2009.

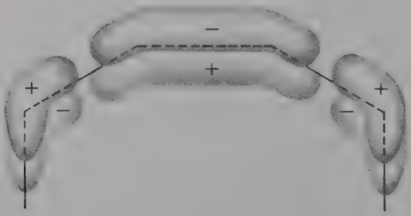
Therefore, in a thermal process, the cyclobutene must open so that on one side the positive lobe lies above the plane, and on the other side below it. Thus the substituents are forced into conrotatory motion:



As mentioned previously, the reverse reaction (butadienes ⟶ cyclobutenes) is rare, but the principle still applies.[195] For the reaction in this direction, the rule is that those lobes of orbitals which overlap must be of the same sign. For thermal cyclization of butadienes, this requires conrotatory motion:



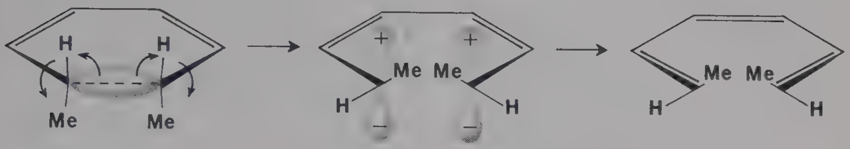
For hexatriene-cyclohexadiene interconversions, the rules predict motions opposite to those for butadiene-cyclobutene interconversions. For a hexatriene, the symmetry of the highest-occupied molecular orbital is



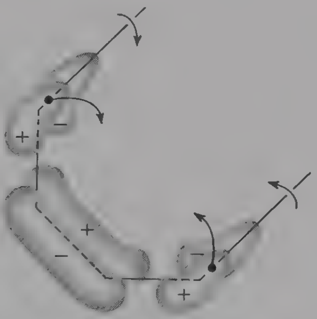
---

[195] Conrotatory motion has been demonstrated in the one known case (Ref. 191).

In the thermal cleavage of cyclohexadienes, then, the positive lobes must lie on the same side of the plane, requiring disrotatory motion:

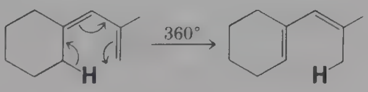


Disrotatory motion is also necessary for the reverse reaction, in order that the orbitals which overlap may be of the same sign:

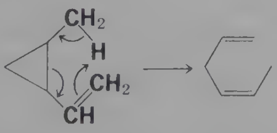


All of these directions are reversed for photochemical processes because in each case a higher orbital, with inverted symmetry, is occupied (see p. 634).

Another rearrangement similar to the Cope is that of 1,3-dienes, e.g.,[196]



Note that this reaction is different from the other reactions considered in this section in that a C—H bond has changed places. Note also that this is actually an internal ene synthesis (reaction **5-14**, p. 601) and that what is essentially the same reaction may be either an addition to a carbon-carbon double bond or a rearrangement. A very similar reaction has a cyclopropane ring replacing one of the double bonds:[197]

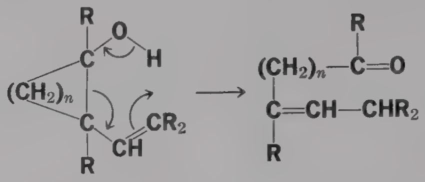


---

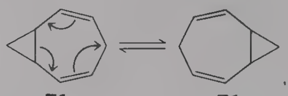
[196] Wolinsky, Chollar, and Baird, *J. Am. Chem. Soc.* **84**, 2775 (1962).

[197] Ellis and Frey, *Proc. Chem. Soc.* **1964**, 221.

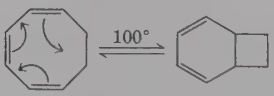
The reverse reaction has also been reported.[198] An analogous rearrangement involving an O—H bond is[199]



It was pointed out earlier that a Cope rearrangement of 1,5-hexadiene gives 1,5-hexadiene. This type of rearrangement, in which the product is equivalent to the starting compound, is called a *degenerate Cope rearrangement.* Another molecule which undergoes a degenerate Cope rearrangement is 3,4-homotropilidene (**71**).[200] At room temperature, the nuclear-magnetic-resonance spectrum of this compound is in accord with the structure shown. At 180° it can be converted by a Cope reaction to a compound equivalent to itself. The interesting thing is that at 180° the nmr spectrum shows that what is existing is an equilibrium mixture of the two structures. That is, at this temperature the molecule rapidly (faster than 10^3 times per second) changes back and forth between the two structures. This is called *valence tautomerism* and is quite distinct from resonance, even though only electrons are shifting.[201] The positions of the nuclei are not the same in the two structures. In valence tautomerism the two structures need not be equivalent. Thus another example of valence tautomerism is illustrated by 1,3,5-cyclooctatriene and bicyclo[4.2.0]octadiene:[202]



71 **71**



At room temperature each isomer is stable, but at about 100° they are in true tautomeric equilibrium, with the mixture consisting of 85% of the monocyclic and 15% of the bicyclic compound.

Molecules like **71** which exhibit valence tautomerism (in this case at 180°) are said to have *fluxional* structures. It may be recalled that *cis*-1,2-

---

[198] Roth and König, *Ann.* **688**, 28 (1965). Also see Grimme, *Chem. Ber.* **98**, 756 (1965).

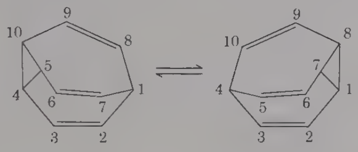
[199] Arnold and Smolinsky, *J. Am. Chem. Soc.* **82**, 4918 (1960).

[200] Doering and Roth, *Tetrahedron* **19**, 715 (1963).

[201] For a review of valence tautomerism, see Schröder, Oth, and Merényi, *Angew. Chem. Intern. Ed. Engl.* **4**, 752–761 (1965).

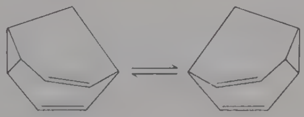
[202] Cope, Haven, Ramp, and Trumbull, *J. Am. Chem. Soc.* **74**, 4867 (1952).

divinylcyclopropane does not exist because it rapidly rearranges to 1,4-cycloheptadiene (p. 835), but in **71** the *cis*-divinylcyclopropane structure is frozen into the molecule in both structures. Two other compounds in which this situation holds are *bullvalene* and *barbaralane.* Bullvalene (**72**) is especially interesting. The Cope rearrangement shown changes the position of the cyclopropane ring from 4,5,10 to 1,7,8. But the molecule could also



72

have undergone rearrangements to put this ring at 1,2,8 or 1,2,7. Any of these could then undergo several Cope rearrangements. In all there are 10!/3, or more than 1.2 million tautomeric forms, and the cyclopropane ring can be at any three carbons which are adjacent. Since each of these tautomers is equivalent to all of the others, this has been called an infinitely degenerate Cope rearrangement. Bullvalene has been synthesized and its nmr spectrum determined.[203] At −25° there are two peaks with an area ratio of 6:4. This is in accord with a single nontautomeric structure. The six are the vinyl protons and the four are the allylic ones. But at 100° the compound shows only one nmr peak, indicating that we have here a truly unique situation, where the compound rapidly interchanges its structure among 1.2 million equivalent forms. In the case of barbaralane (bullvalene in which one CH=CH has been replaced by a CH_2):



there are only two equivalent tautomers.[204] However, nmr spectra indicate that even at room temperature a rapid interchange of both tautomers is present, though by about −100° this has slowed to the point where the spectrum is in accord with a single structure. Corresponding behavior, both at 25° and at −100°, is exhibited by substituted barbaralanes, in which the CH_2 group is replaced by CHOH, CHCl, CO, and $C(SR)_2$.[205] In the case of

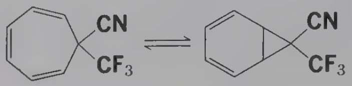
---

[203] Schröder, *Angew. Chem. Intern. Ed. Engl.* **2,** 481 (1963), *Chem. Ber.* **97,** 3140 (1964); Merényi, Oth, and Schröder, *Chem. Ber.* **97,** 3150 (1964). See also Doering *et al.*, Ref. 204. For the synthesis and properties of substituted bullvalenes, see Oth, Merényi, Nielsen, and Schröder, *Chem. Ber.* **98,** 3385 (1965); Oth, Merényi, Engel, and Schröder, *Tetrahedron Letters* **1966,** 3377; Vogel, Grimme, Meckel, Riebel, and Oth, *Angew. Chem. Intern. Ed. Engl.* **5,** 590 (1966); and Doering *et al.*, Ref. 204. For a review of bullvalenes, see Schröder and Oth, *Angew. Chem. Intern. Ed. Engl.* **6,** 414–423 (1967).

[204] Barbaralane was synthesized by Biethan, Klusacek, and Musso, *Angew. Chem. Intern. Ed. Engl.* **6,** 176 (1967); by Tsuruta, Kurabayashi, and Mukai, *Tetrahedron Letters* **1967,** 3775; and by Doering, Ferrier, Fossel, Hartenstein, Jones, Klumpp, Rubin, and Saunders, *Tetrahedron* **23,** 3943 (1967).

[205] Lambert, *Tetrahedron Letters* **1963,** 1901; Doering *et al.*, Ref. 204.

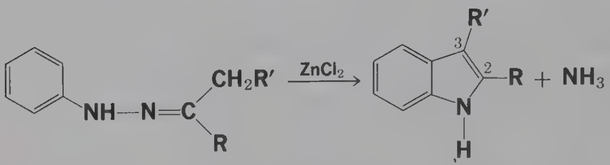
7-cyano-7-trifluoromethyl-1,3,5-cycloheptatriene (**73**), nmr spectra indicate that here too at room temperature there is a true valence tautomerism.[206] In this case one isomer (**74**) has the *cis*-1,2-divinylcyclopropane structure while the other does not.



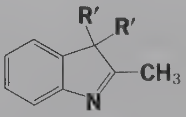
73 **74**

OS **43,** 17, 71. Also see OS **III,** 807.

8-27 The Fischer indole synthesis



When arylhydrazones of aldehydes or ketones are treated with a catalyst, elimination of ammonia takes place, and an indole is formed, in a reaction called the *Fischer indole synthesis.*[207] Zinc chloride is the catalyst most frequently employed, but dozens of others, including other metal halides, proton and Lewis acids, and certain transition metals have also been used. Arylhydrazones are easily prepared by the treatment of aldehydes or ketones with phenylhydrazine (reaction **6-21,** p. 674). However, it is not necessary to isolate the arylhydrazone. The arylhydrazine may be treated with a mixture of the aldehyde or ketone and the catalyst. In order to get an indole, the aldehyde or ketone must be of the form $RCOCH_2R'$ (R = alkyl, aryl, or hydrogen). When R is hydrogen or methyl, then this group is always found at the 2-position of the indole, and R′ at the 3-position. However, arylhydrazones of acetaldehyde do not give the reaction. When the aldehyde or ketone is of the form $CH_3COCHR'_2$ ($R' \neq$ hydrogen), then the product is **75**. For compounds of the form $RCH_2COCHR'_2$, a mixture of both types is obtained.



75

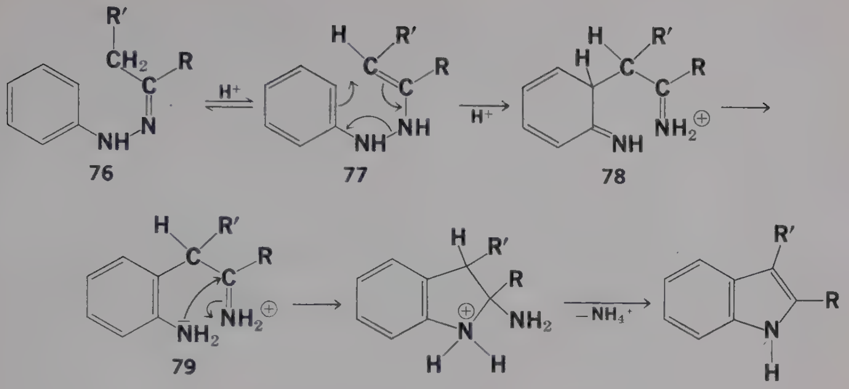
At first glance the reaction does not seem to be a rearrangement. However, the key step of the mechanism is the same as that of the Claisen or Cope rearrangement:[208]

---

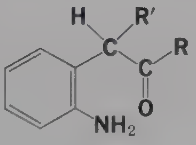
[206] Ciganek, *J. Am. Chem. Soc.* **87,** 1149 (1965).

[207] For a review, see Robinson, *Chem. Rev.* **63,** 373–401 (1963).

[208] This mechanism was proposed by Robinson and Robinson, *J. Chem. Soc.* **113,** 639 (1918).



There is much evidence for this mechanism; for example: (1) the isolation of **79** in several instances;[209] (2) the isolation of side products which could only have come from **78**;[210] and (3) ^{15}N labeling experiments, which showed that it was the nitrogen farther from the ring which was eliminated as ammonia.[211] Alternatively it is possible that **79** is first hydrolyzed to **80** before cyclization

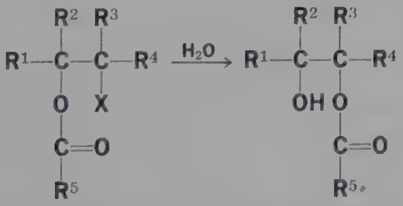


80

occurs. The main function of the catalyst seems to be to speed the conversion of **76** to **77**. The reaction can be performed without a catalyst.

OS **III**, 725; **IV**, 884. Also see OS **IV**, 657.

8-28 Acyl rearrangements



$$R^1-\underset{\underset{\underset{R^5}{|}}{\overset{|}{\underset{|}{O}}\atop C=O}}{\overset{\overset{R^2}{|}}{C}}-\underset{\underset{X}{|}}{\overset{\overset{R^3}{|}}{C}}-R^4 \xrightarrow{H_2O} R^1-\underset{\underset{OH}{|}}{\overset{\overset{R^2}{|}}{C}}-\underset{\underset{\underset{R^5}{|}}{\overset{|}{\underset{|}{O}}\atop C=O}}{\overset{\overset{R^3}{|}}{C}}-R^4$$

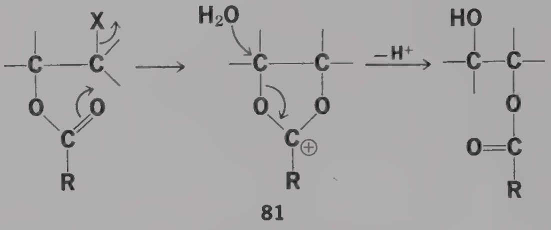
There are two basic kinds of acyl rearrangements. One of these, illustrated above, involves migration of an acyloxy group to a position formerly occupied by a leaving group, and the replacement of the acyloxy group by a nucleophile. The reaction is similar in appearance to reaction **8-11**, but the mechanism is not entirely the same. The acyloxy group does replace the leaving group in an S_N2 process, and is replaced in turn by another S_N2 process (as in reaction **8-11**), but it is not the alkyl oxygen which is attacking, but the acyl oxygen; that is, the transition state is five-membered and not three-membered:

---

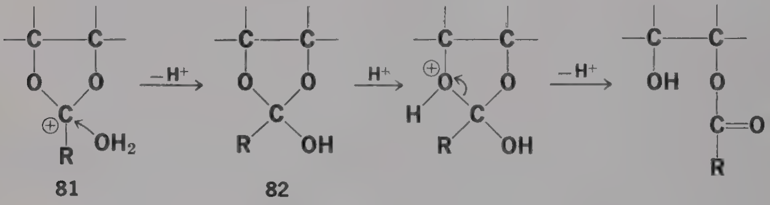
[209] For example, Suvorov, Sorokina, and Sheinker, *J. Gen. Chem. USSR* **28**, 1058 (1958).

[210] Robinson and Brown, *Can. J. Chem.* **42**, 1940 (1964).

[211] Clausius and Weisser, *Helv. Chim. Acta* **35**, 400 (1952).

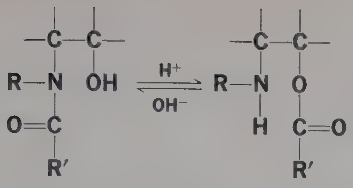


81 may be opened in two ways: (1) attack by the nucleophile at that position which is more favorable, the reaction thus becoming either a nucleophilic substitution by the neighboring-group mechanism or a rearrangement (this path is shown above) or (2) attack at the *carbonyl* carbon:

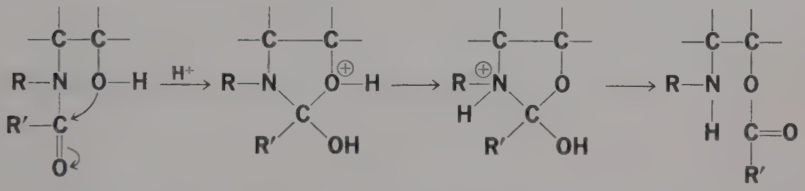


Of course, ring opening in the other direction gives the substitution and not the rearrangement product. When the nucleophile is water, then rearrangement by path (1) or by path (2) gives the same product and similarly for substitution. The paths may be told apart by the difference in stereochemical consequences. For rearrangement, path (1) requires inversion at both carbons, while path (2) requires retention at the migration origin (C-1) and inversion at the terminus (C-2). Substitution by path (1) involves retention at both carbons, while path (2) predicts retention at C-1 and inversion at C-2. The leaving group may be halo, OTs, OH_2^+, or any other good S_N leaving group. Besides water, the nucleophile may be ROH or RCOOH, in which case OR or OCOR appears in the product instead of OH. However, with these nucleophiles the reaction proceeds only by path (1), or if it does take path (2), then the reaction stops at the ortho ester stage (**82,** with OR or OCOR instead of OH). Analogous reactions have been carried out with nitrogen or sulfur replacing one or both of the acyloxy oxygens.

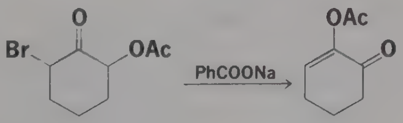
In the second type of acyl rearrangement, there is a 1,4-migration from one hetero atom to another, e.g.,



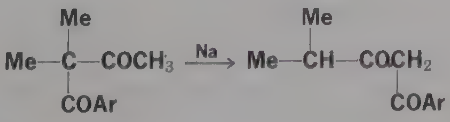
This type of reaction is undergone by N- or O-acylated amino alcohols and conceivably by monoacylated 1,2-diamines or 1,2-glycols and the sulfur analogs of these compounds, though not many of these possibilities have been examined. The mechanism here is



In this particular case, nitrogen-to-oxygen migration may be accomplished with acids (which stabilize the amine as the salt) and the reverse oxygen-to-nitrogen migration with bases. The stereochemistry must involve retention at both carbons. These reactions are actually internal examples of alcoholysis of amides (p. 323) and of acylation of amines by esters (reaction **0-54**, p. 338). Transannular rearrangements of this type have also been reported. A similar reaction involves migration to the oxygen of a carbonyl group, and concomitant elimination:[212]



Other more mysterious acyl rearrangements are known; e.g.,[213]



$$\mathrm{Me{-}\overset{Me}{\underset{COAr}{C}}{-}COCH_3 \xrightarrow{Na} Me{-}\overset{Me}{CH}{-}CO\underset{COAr}{C}H_2}$$

There are no *Organic Syntheses* references, but see OS **42,** 69, for a related reaction.

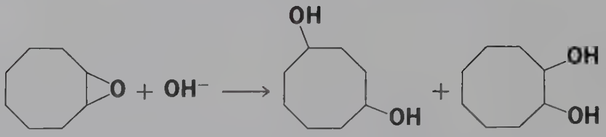
---

[212] Bordwell and Wellman, *J. Org. Chem.* **28,** 1347 (1963), **31,** 351 (1966).

[213] Bromham and Pinder, *J. Chem. Soc.* **1959,** 2688.

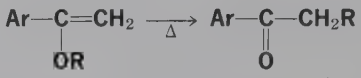
B. Noncyclic rearrangements

8-29 Hydride shifts



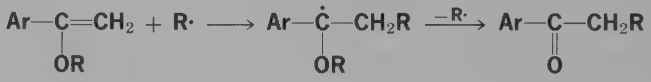
The above is a typical example of a transannular hydride shift. The 1,2-glycol is formed by a normal epoxide hydrolysis reaction (**0-8**, p. 307). For a discussion of 1,3- and longer hydride shifts, see page 788.

8-30 Rearrangement of vinyl ethers



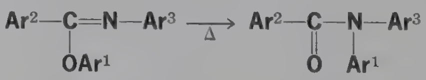
$$\underset{\displaystyle OR}{Ar-\underset{|}{C}=CH_2} \xrightarrow[\Delta]{} Ar-\underset{\displaystyle O}{\underset{\|}{C}}-CH_2R$$

When vinyl ethers of the form $ArC(OR)=CH_2$ are heated, they rearrange to ketones. This is a 1,3-shift of R from O to C. It is an intermolecular process and involves free radicals.[214] After some type of initiation step, the propagation steps are



$$\underset{\displaystyle OR}{Ar-\underset{|}{C}=CH_2} + R\cdot \longrightarrow \underset{\displaystyle OR}{Ar-\underset{|}{\dot{C}}-CH_2R} \xrightarrow{-R\cdot} Ar-\underset{\displaystyle O}{\underset{\|}{C}}-CH_2R$$

8-31 The Chapman rearrangement



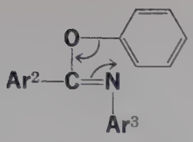
$$\underset{\displaystyle OAr^1}{Ar^2-\underset{|}{C}=N-Ar^3} \xrightarrow[\Delta]{} Ar^2-\underset{\displaystyle O}{\underset{\|}{C}}-\underset{\displaystyle Ar^1}{\underset{|}{N}}-Ar^3$$

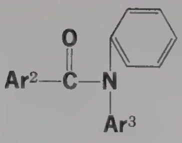
In the *Chapman rearrangement,* N,N-diaryl amides are formed when aryl imidates are heated. The reaction is similar in appearance to reaction **8-30**.[215] Many groups may be present in the rings, for example, alkyl, halo, OR, CN, COOR, etc. Aryl migrates best when it contains electron-withdrawing groups. On the other hand, electron-withdrawing groups in Ar^2 or Ar^3 decrease the reactivity. The products may be hydrolyzed to diarylamines, and this is a method for preparing these compounds. The mechanism is different from that of reaction **8-30** and features a four-membered cyclic transition state:

---

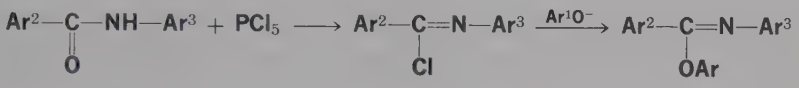
[214] Wiberg, Kintner, and Motell, *J. Am. Chem. Soc.* **85**, 450 (1963), and references cited therein.

[215] For a review, see Schulenberg and Archer, *Org. Reactions* **14**, 1–51 (1965).





resulting in a 1,3-oxygen-to-nitrogen shift. Imidates may be prepared from N-aryl amides in the following manner:

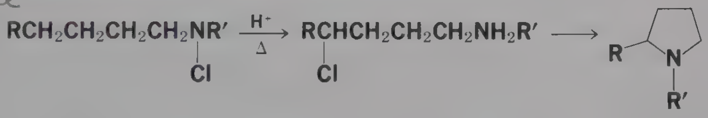


$$\underset{\parallel\atop O}{Ar^2—C}—NH—Ar^3 + PCl_5 \longrightarrow \underset{|\atop Cl}{Ar^2—C}=N—Ar^3 \xrightarrow{Ar^1O^-} \underset{|\atop OAr}{Ar^2—C}=N—Ar^3$$

Imidates with any or all of the three groups being alkyl also rearrange, but they require catalysis by H_2SO_4 or a trace of methyl iodide or methyl sulfate. The mechanism is different, however, involving an intermolecular process. This is also true for derivatives of formamide ($Ar^2 = H$).

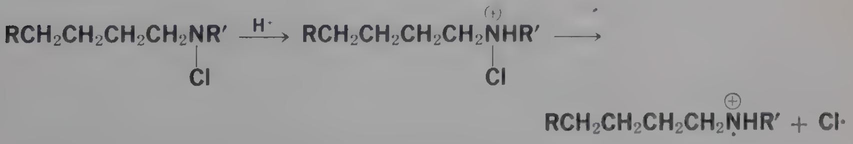
8-32 The Hofmann-Löffler and related reactions

Radical



When N-haloamines in which one alkyl group has a hydrogen in the 4- or 5-position are heated with sulfuric acid, pyrrolidines or piperidines are formed, in a reaction known as the *Hofmann-Löffler reaction.*[216] R′ is normally alkyl, but the reaction has been extended to R′ = H by use of concentrated sulfuric acid solution.[217] The first step of the reaction is a rearrangement, with the halogen migrating from the nitrogen to the 4- or 5-position of the alkyl group. It is possible to isolate the resulting haloamine salt, but usually this is not done, and the second step, the ring closure (reaction **0-44**, p. 331), takes place. Though the reaction is most often induced by heat, this is not necessary, and irradiation and chemical initiators (e.g., peroxides) have been used instead. The mechanism is of a free-radical type, with the main step involving an internal hydrogen abstraction:[218]

Initiation:



$$RCH_2CH_2CH_2CH_2\underset{|\atop Cl}{N}R' \xrightarrow{H^+} RCH_2CH_2CH_2CH_2\underset{|\atop Cl}{\overset{(+)}{N}}HR' \longrightarrow$$

$$RCH_2CH_2CH_2CH_2\overset{\oplus}{\dot{N}}HR' + Cl\cdot$$

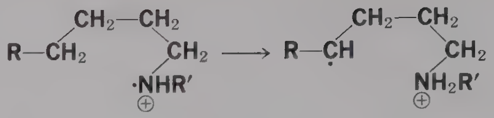
---

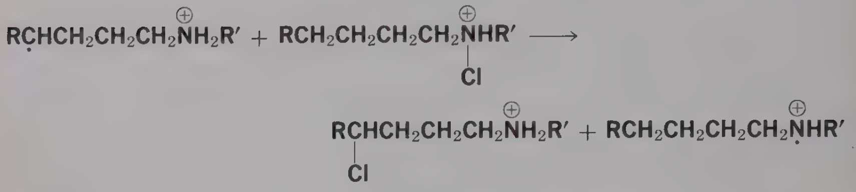
[216] For a review, see Wolff, *Chem. Rev.* **63**, 55–64 (1963).

[217] Schmitz and Murawski, *Chem. Ber.* **99**, 1493 (1966).

[218] Wawzonek and Thelan, *J. Am. Chem. Soc.* **72**, 2118 (1950).

Propagation:

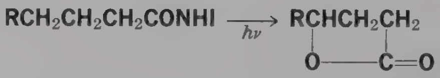




$$R\underset{\cdot}{C}HCH_2CH_2CH_2\overset{\oplus}{N}H_2R' + RCH_2CH_2CH_2CH_2\overset{\oplus}{\underset{Cl}{N}}HR' \longrightarrow \underset{Cl}{RCH}CH_2CH_2CH_2\overset{\oplus}{N}H_2R' + RCH_2CH_2CH_2CH_2\overset{\oplus}{\underset{\cdot}{N}}HR'$$

etc.

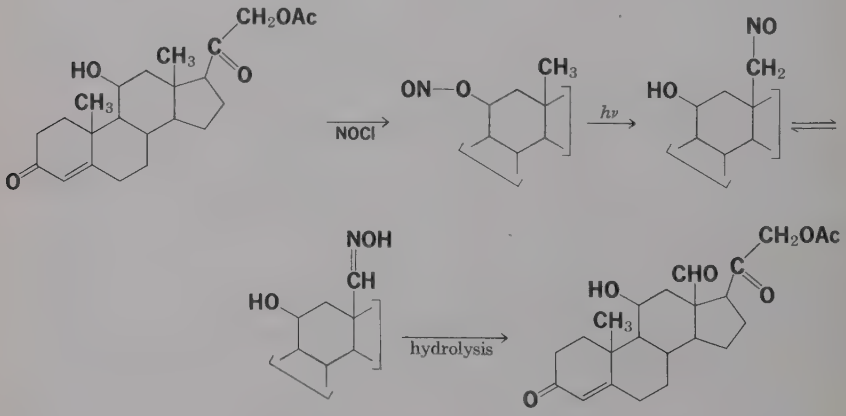
A similar reaction has been carried out on N-halo amides, which give γ-lactones:[219]



$$RCH_2CH_2CH_2CONHI \xrightarrow[h\nu]{} \underset{O\text{——}C{=}O}{RCHCH_2CH_2}$$

Radical

Another related reaction is the *Barton reaction,* by means of which a methyl group in the γ position to an OH group can be oxidized to a CHO group. The alcohol is first converted to the nitrite ester. Photolysis of the nitrite results in conversion of the nitrite group to the OH group, and nitrosation of the methyl group. Hydrolysis of the oxime tautomer gives the aldehyde, e.g.,[220]

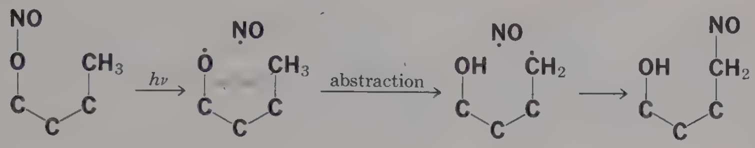


---

[219] Barton, Beckwith, and Goosen, *J. Chem. Soc.* **1965**, 181; Petterson and Wambsgans, *J. Am. Chem. Soc.* **86,** 1648 (1964); Neale, Marcus, and Schepers, *J. Am. Chem. Soc.* **88,** 3051 (1966).

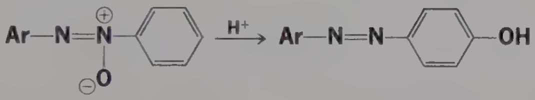
[220] Barton and Beaton, *J. Am. Chem. Soc.* **83,** 4083 (1961); also see Barton, Beaton, Geller, and Pechet, *J. Am. Chem. Soc.* **82,** 2640 (1960).

This reaction takes place only when the methyl group is in a favorable steric position. The mechanism is similar to that of the Hofmann-Löffler reaction:[221]

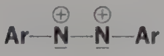


OS **III**, 159.

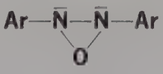
8-33 The Wallach rearrangement



The conversion of azoxy compounds, upon acid treatment, to *p*-hydroxy azo compounds (or sometimes the *o*-hydroxy isomers) is called the *Wallach rearrangement.* The mechanism is not settled. When the reaction was carried out with an azoxy compound in which the N—O nitrogen was labeled with ^{15}N, *both* nitrogens of the product carried the label equally,[222] demonstrating that the oxygen did not have a preference for migration to either the near or the far ring. This shows that there is a symmetrical intermediate, but just what kind is uncertain. Both a dication intermediate (**83**)[223] and a cyclic intermediate (**84**)[222] have been proposed, and there is evidence for



83



84

each.[224] Kinetic studies have shown that the original azoxy compound is diprotonated before it undergoes further reaction.[225] These studies are consistent with a mechanism in which a diprotonated **84** is formed, and then converted by loss of water to **83**, which is attacked in one ring by an oxygen-containing nucleophile. However, the mechanism seems to be different when electron-donating groups are present.

---

[221] Kabasakalian and Townley, *J. Am. Chem. Soc.* **84,** 2711 (1962); Akhtar, Barton, and Sammes, *J. Am. Chem. Soc.* **87,** 4601 (1965).

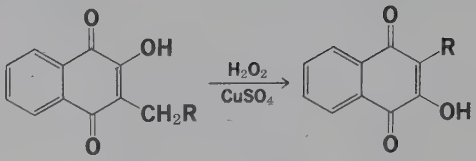
[222] Shemyakin, Maimind, and Vaichunaite, *Chem. Ind. (London)* **1958,** 755, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1960,** 808. Also see Behr and Hendley, *J. Org. Chem.* **31,** 2715 (1966).

[223] Gore, *Chem. Ind. (London)* **1959,** 191.

[224] The dication intermediate is supported by Buncel and Lawton, *Can. J. Chem.* **43,** 862 (1965); the other by Shemyakin, Maimind, and Agadzhanyan, *Chem. Ind. (London)* **1961,** 1223; and Shemyakin, Agadzhanyan, Maimind, and Kudryavtsev, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963,** 1216.

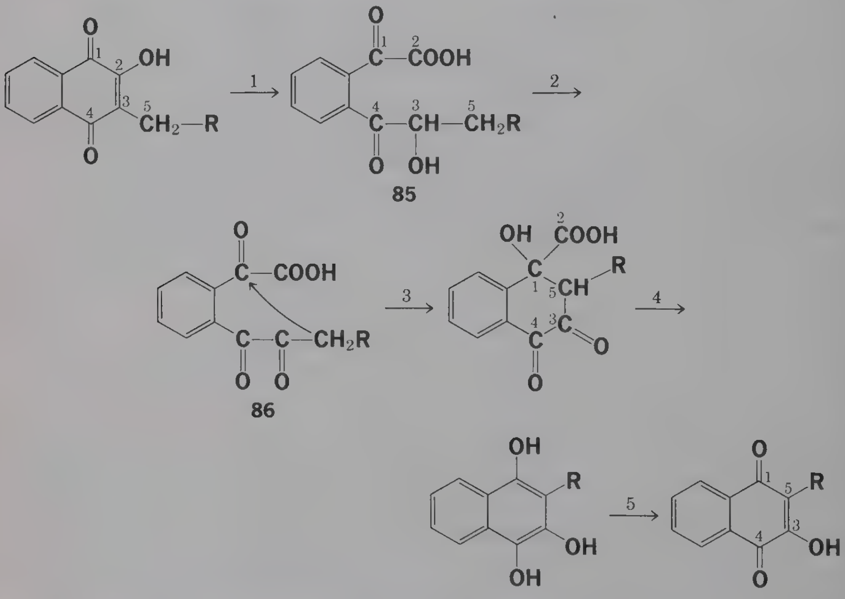
[225] Hahn, Lee, and Jaffé, *J. Am. Chem. Soc.* **89,** 4975 (1967).

8-34 The Hooker oxidation



This reaction of substituted naphthoquinones, which takes place in high yield, is called the *Hooker oxidation*.[226] If R is primary, the reaction may be repeated. In this way *n*-alkyl groups may be brought down, one carbon at a time, until only H is left. R may contain double bonds, which are undisturbed under these conditions. The reaction may be performed with H_2O_2 and copper sulfate or $KMnO_4$ and atmospheric oxygen.

The mechanism[227] involves: (1) oxidative ring cleavage, (2) oxidation of an alcohol to a ketone, (3) an internal aldol condensation, (4) an oxidative decarboxylation and an aromatization, and (5) an oxidation to the quinone:



Thus the carbon which is lost from the molecule is the original C-2, and the original methylene group (C-5) ends up in the ring. The intermediates **85** and **86** have been isolated.

---

[226] For a review, see Shemyakin and Shchukina, *Quart. Rev. (London)* **10**, 261–282 (1956), pp. 276–280.

[227] Proposed by Fieser and Fieser, *J. Am. Chem. Soc.* **70**, 3215 (1948).

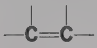
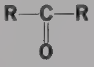
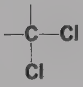
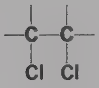
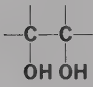
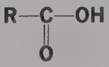
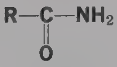
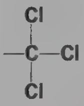
CHAPTER NINETEEN

Oxidations and Reductions

First we must examine what we mean when we speak of oxidation and reduction. Inorganic chemists define oxidation in two ways: loss of electrons and increase in oxidation number. In organic chemistry, these definitions, while still technically correct, are not easy to apply. While electrons are directly transferred in some organic oxidations and reductions (see p. 855), the mechanisms of most of these reactions do not involve a direct electron transfer. As for oxidation number, while this is easy to apply in some cases, e.g., the oxidation number of carbon in CH_4 is -4, in most cases attempts to apply the concept lead to fractional values or apparent absurdities. Thus, carbon in propane has an oxidation number of -2.67 and in butane of -2.5, though organic chemists seldom think of these two compounds as being in different oxidation states. An improvement could be made by assigning different oxidation states to different carbon atoms in a molecule, depending on what is bonded to them (for example, the two carbons in acetic acid are obviously in different oxidation states), but for this a whole set of arbitrary assumptions would be required, since the oxidation number of an atom in a molecule is assigned on the basis of the oxidation numbers of the atoms attached to it. There would seem little to be gained by such a procedure. What the organic chemists have done—though more by custom than by any formal agreement—is to set up a series of functional groups, in a qualitative way, arranged in order of increasing oxidation state, and then to define oxidation as *the conversion of a functional group in a molecule from one category to a higher one.* Reduction is the opposite. For the simple functional groups this series is shown in Table 1. It should be noted that this classification applies only to a single carbon atom or to two adjacent carbon atoms. Thus 1,3-dichloropropane is in the same oxidation state as methyl chloride, but 1,2-dichloropropane is in a higher one. Obviously such distinctions are somewhat arbitrary, and if we attempt to carry them too far, we shall find ourselves painted into a corner. Nevertheless the basic idea will serve us well. It should be noted that conversion of any compound to another in the same category is not an oxidation or a reduction. Most oxidations in organic chemistry involve a gain of oxygen and/or a loss of hydrogen. The reverse is true for reductions.

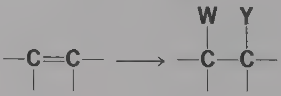
Of course, there is no oxidation without a concurrent reduction. However, we classify reactions as oxidations or reductions depending on whether the *organic compound* is oxidized or reduced. In some cases both the oxidant and reductant are organic, and we shall consider those reactions separately.

TABLE 1. Categories of simple functional groups arranged according to oxidation state
Oxidation is the conversion of a functional group in a molecule to a higher category; reduction is conversion to a lower one. Conversions within a category are neither oxidations nor reductions. The numbers given at the bottom are only approximations

RH	 $-\overset{\vert}{C}=\overset{\vert}{C}-$ ROH RCl RNH_2 etc.	$-C\equiv C-$  $R-\underset{O}{\underset{\Vert}{C}}-R$  $-\overset{\vert}{\underset{Cl}{\underset{\vert}{C}}}-Cl$  $-\overset{\vert}{\underset{Cl}{\underset{\vert}{C}}}-\overset{\vert}{\underset{Cl}{\underset{\vert}{C}}}-$  $-\overset{\vert}{\underset{OH}{\underset{\vert}{C}}}-\overset{\vert}{\underset{OH}{\underset{\vert}{C}}}-$ etc.	 $R-\underset{O}{\underset{\Vert}{C}}-OH$  $R-\underset{O}{\underset{\Vert}{C}}-NH_2$  $-\overset{Cl}{\overset{\vert}{\underset{Cl}{\underset{\vert}{C}}}}-Cl$ etc.	CO_2 CCl_4
Approximate oxidation numbers				
−4	−2	0	+2	+4

MECHANISMS

It must be noted that our definition of oxidation has nothing to do with mechanism. Thus the conversion of methyl bromide to methanol with KOH (reaction **0-1**, p. 303) and to methane with $LiAlH_4$ (reaction **0-73**, p. 348) have the same S_N2 mechanisms, but one is a reduction (according to our definition) and the other is not. It is impractical to consider the mechanisms of oxidation and reduction reactions in broad categories in this chapter as we have done for the reactions considered in Chapters 10 to 18.[1] The main reason is that the mechanisms are too diverse, and this in turn is because the bond changes are too different. For example, in Chapter 15, all of the reactions involved the following bond change (with respect to the substrate):



$$-\underset{|}{C}=\underset{|}{C}- \longrightarrow -\overset{W}{\overset{|}{\underset{|}{C}}}-\overset{Y}{\overset{|}{\underset{|}{C}}}-$$

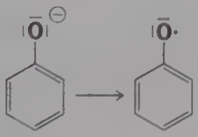
---

[1] For monographs on oxidation mechanisms, see Wiberg, "Oxidation in Organic Chemistry," 2 vols., Academic Press Inc., New York, 1965; Waters, "Mechanisms of Oxidation of Organic Compounds," John Wiley & Sons, Inc., New York, 1964; and Stewart, "Oxidation Mechanisms," W. A. Benjamin, Inc., New York, 1964. For a review, see Wiberg, *Surv. Progr. Chem.* **1**, 211–248 (1963).

and a relatively few mechanisms covered all of the reactions. But for oxidations and reductions the bond changes are far more diverse. Another reason is that the mechanism of a given oxidation or reduction reaction often varies greatly with the oxidizing or reducing agent employed. Very often the mechanism has been studied intensively for only one or a few of many possible agents. A third reason is closely related: as a class, less work has been done on the mechanisms of oxidation-reduction reactions than on the reactions covered in previous chapters. However, in recent years the pace in the area has been increasing rapidly, and it is likely that before long this reason will no longer apply.

Although we therefore shall not cover oxidation and reduction mechanisms in the same way as we have covered other mechanisms, it is still possible to list a few broad mechanistic categories. In doing this, we follow the scheme of Wiberg.[2]

1. *Direct electron transfer.* We have already met a few reactions in which the reduction is actually a direct gain of electrons or the oxidation a direct loss of them. An example is the Birch reduction (reaction **5-12**, p. 597), where sodium directly transfers an electron to an aromatic ring. An example from this chapter is found in the bimolecular reduction of ketones (reaction **9-57**), where again it is a metal which supplies the electrons. This kind of mechanism is found largely in three types of reaction:[3] (1) the oxidation or reduction of a free radical (oxidation to a positive or reduction to a negative ion); (2) the oxidation of a negative ion or the reduction of a positive ion to a comparatively stable free radical; and (3) electrolytic oxidations or reductions (an example being the Kolbe reaction, **4-25**, p. 557). An important example of the second type is oxidation of amines and phenolate ions:



These reactions occur easily because of the relative stability of the radicals involved.

2. *Hydride transfer.*[4] In some reactions a hydride ion is transferred to or from the substrate. The reduction of epoxides with $LiAlH_4$ is an example (reaction **0-76**, p. 350). Another is the Cannizzaro reaction (**9-62**), in which one organic species transfers a hydride ion to another and is itself oxidized, while the other is reduced. Reactions in which a carbonium ion abstracts a hydride ion belong in this category:

$$R^+ + R'H \longrightarrow RH + R'^+$$

---

[2] Wiberg, *Surv. Progr. Chem.* **1,** 211–248 (1963).

[3] Littler and Sayce, *J. Chem. Soc.* **1964**, 2545.

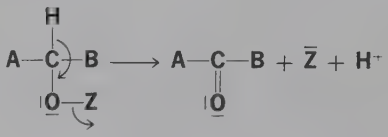
[4] For reviews, see Deno, Peterson, and Saines, *Chem. Rev.* **60,** 7–14 (1960); Kursanov and Parnes, *Russ. Chem. Rev.* **30,** 598–602 (1961).

3. *Hydrogen-atom transfer.* Many oxidation and reduction reactions are free-radical substitutions and involve the transfer of a hydrogen atom. For example, one of the two main propagation steps of reaction **4-1** (p. 532) involves proton abstraction:

$$\mathrm{RH} + \mathrm{Cl}\cdot \longrightarrow \mathrm{R}\cdot + \mathrm{HCl}$$

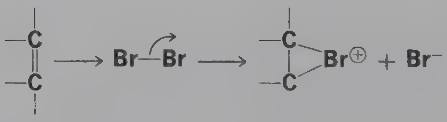
This is the case for many of the reactions of Chapter 14.

4. *Formation of ester intermediates.* A number of oxidations involve the formation of an ester intermediate (usually of an inorganic acid), and then the cleavage of this intermediate:

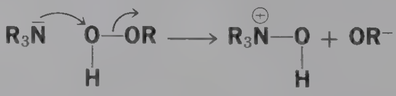


Z is usually CrO_3H, MnO_3, or a similar inorganic acid moiety. One example of this mechanism was seen in reaction **4-6** (p. 539), where A was an alkyl or aryl group, B was OH, and Z was CrO_3H. Another is the oxidation of a secondary alcohol to a ketone (reaction **9-3**), where A and B are alkyl or aryl groups and Z is also CrO_3H. In the lead tetraacetate oxidation of glycols (reaction **9-8**) the mechanism also follows this pattern, but the positive leaving group is carbon instead of hydrogen. It should be noted that the cleavage shown is actually an example of an E2 elimination mechanism. Reaction **7-34** (p. 778) is another example.

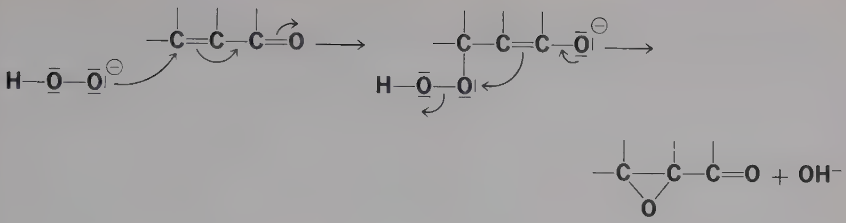
5. *Displacement mechanisms.* In these reactions the organic substrate uses its electrons to cause displacement on an electrophilic oxidizing agent. One example is the addition of bromine to an olefin (reaction **5-22**, p. 610).



An example from this chapter is found in reaction **9-25**:



6. *Addition-elimination mechanisms.* In the reaction between α,β-unsaturated ketones and alkaline peroxide (reaction **5-29**, p. 618), the oxidizing agent adds to the substrate, and then part of it is lost:



In this case the oxygen of the oxidizing agent was in oxidation state -1 and the OH^- departed with its oxygen in the -2 state, so it was reduced and the substrate oxidized. There are several reactions which follow this pattern of addition of an oxidizing agent, and the loss of part of the agent, usually in a different oxidation state. Another example is the oxidation of ketones with SeO_2 (reaction **9-16**). This reaction is also an example of category 4, since it involves formation and E2 cleavage of an ester. This example shows that these six categories are not mutually exclusive.

REACTIONS

In this chapter, the reactions are classified by the type of bond change occurring to the organic substrate, in conformity with our practice in the other chapters. This means that there is no discussion in any one place of the use of a particular oxidizing or reducing agent, e.g., acid dichromate or $LiAlH_4$ (except for a discussion of selectivity of reducing agents, p. 890). Some oxidizing or reducing agents are fairly specific in their action, attacking only one or a few types of substrate. Others, like acid dichromate, permanganate, $LiAlH_4$, and catalytic hydrogenation, are much more versatile.[5]

When an oxidation or a reduction could be considered in a previous chapter, this was done. For example, the catalytic hydrogenation of olefins is a reduction, but it is also an addition to the C=C bond and was treated in Chapter 15. In this chapter are discussed only those reactions which do not fit into the nine categories of Chapters 10 to 18. An exception to this rule was made for reactions which involve elimination of hydrogen (**9-1** to

[5] For reviews on the behavior of certain oxidizing agents, see Ladbury and Cullis, *Chem. Rev.* **58,** 403–438 (1958), pp. 425–431 (permanganate); Thyagarajan, *Chem. Rev.* **58,** 439–460 (1958) (ferricyanide); Evans, *Quart. Rev. (London)* **13,** 61–70 (1959) (MnO_2); Waters, *Quart. Rev. (London)* **12,** 277–300 (1958) (chromic acid and permanganate); Littler and Waters, *J. Chem. Soc.* **1959,** 1299–1305 (pentavalent vanadium); Bacon, *Chem. Ind. (London)* **1962,** 19–22 (metal ions); Manly, *Chem. Ind. (London)* **1962,** 12–18 (hydrogen peroxide); Bailey, *Chem. Rev.* **58,** 925–1010 (1958) (ozone); and Criegee, in Foerst, "Newer Methods of Preparative Organic Chemistry," vol. 2, pp. 367–388, Academic Press Inc., New York, 1963 [reprinted from *Angew. Chem.* **70,** 173–179 (1958)] (lead tetraacetate). Also see Waters, in Gilman, "Advanced Organic Chemistry," vol. IV, pp. 1120–1245, John Wiley & Sons, Inc., New York, 1953. For reviews on the behavior of certain reducing agents, see Rausch, McEwen, and Kleinberg, *Chem. Rev.* **57,** 417–437 (1957) (unipositive magnesium); Popp and Schultz, *Chem. Rev.* **62,** 19–40 (1962) (cathodic reductions); and Jackman, *Advan. Org. Chem.* **2,** 329–366 (1960) (reductions in which the hydrogen comes from an organic molecule). For a treatise on reductions with metal hydrides, see Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, 1956. Also see House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, 1965.

TABLE 2. Reactions commonly regarded as oxidations which were treated in earlier chapters

A. Reactions of the type **R—H** or **R—M** (metal) ⟶ **R—OH, ROR′, ROOH,** etc.

1-29	p. 426
1-30	p. 426
2-15	p. 471
2-16	p. 472
2-17	p. 472
3-20	p. 511
3-28	p. 519
4-4	p. 538
4-5	p. 538
4-6	p. 539
4-7	p. 542
4-8	p. 543
4-9	p. 545
4-10	p. 545

B. Addition of two oxygens to a double bond

5-28	p. 616
5-29	p. 618
5-30	p. 621

C. Other oxidations

4-25	p. 557	Kolbe reaction
4-26	p. 559	Hunsdiecker reaction
7-34	p. 778	Oxidation of nitrates to aldehydes
8-20	p. 822	Baeyer-Villiger rearrangement
8-34	p. 852	Hooker oxidation

TABLE 3. Some reactions not commonly considered to be oxidations, but which fit our definition, which were treated in earlier chapters

A. Reactions in which an **R—H** or **R—M** bond is converted to an **R—N, R—S,** or **R**—halogen bond

1-2–1-11	p. 396
1-33–1-36	p. 430
1-42	p. 438
2-4–2-8	p. 458
2-18–2-19	p. 473
2-30	p. 482
3-18–3-19	p. 510
4-1–4-3	p. 532
4-11–4-12	p. 546

B. Addition of two hetero atoms to a double bond

5-22–5-25	p. 610
5-32–5-33	p. 622

C. Reactions of the type **RH** + **RH** ⟶ **RR** or **RM** + **RM** ⟶ **RR**

4-13	p. 548
4-14	p. 549
4-22	p. 555

TABLE 4. Reactions commonly regarded as reductions which were treated in earlier chapters

A. Reactions in which a **C—N, C—O, C—S,** or **C**—halogen bond is replaced by a **C—H** bond

0-73	p. 348	**0-80**	p. 352
0-74	p. 349	**0-103**	p. 374
0-75	p. 350	**1-43**	p. 438
0-76	p. 350	**3-9**	p. 505
0-77	p. 350	**3-10**	p. 505
0-78	p. 351	**3-25**	p. 513
0-79	p. 352	**4-24**	p. 556

B. Additions of **H** and **H** to multiple bonds

5-11	p. 591
5-12	p. 597
6-27	p. 678
6-28	p. 682
6-29	p. 683
6-68	p. 725

C. Other reductions

5-13	p. 599	Hydroboration
5-17	p. 607	Reductive coupling of olefins
6-7	p. 663	Reductive alkylation of alcohols
6-16	p. 668	Reductive alkylation of ammonia or amines
6-30	p. 684	Reduction of nitriles to aldehydes
7-11	p. 763	Decomposition of toluene-*p*-sulfonates

9-7), which were not treated in Chapter 17 because the mechanisms generally differ from those in that chapter. Table 2 is a list of those reactions, previously treated, which are commonly regarded as oxidations. Many other reactions are not commonly regarded as oxidations, and yet they fit our definition. Some of these which have been treated in other chapters are listed in Table 3. Tables 4 and 5 are similar lists of reductions.

Oxidations. The reactions in this section are classified into groups depending on the type of bond change involved. These groups are: eliminations of hydrogen, reactions involving cleavage of carbon-carbon bonds, reactions involving replacement of hydrogen by oxygen, reactions in which an unshared pair becomes bonded to oxygen, oxidative coupling, and oxidation to inorganic esters. Tables 2 and 3 list oxidations which were treated in previous chapters.

A. Eliminations of hydrogen

9-1 Aromatization of six-membered rings

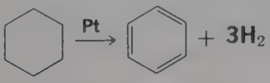


TABLE 5. Some reactions not commonly considered to be reductions, but which fit our definition, which were treated in earlier chapters

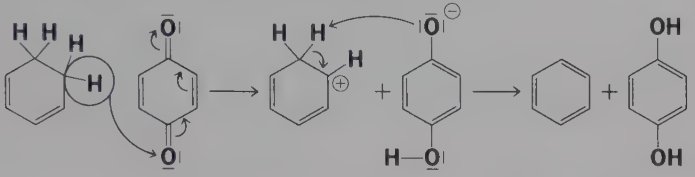
A. Replacement of **S**, **N**, halogen, by **H** or **M**	
1-44	p. 439
1-45	p. 439
1-46	p. 440
2-24	p. 475
2-25	p. 476
B. Elimination of two hetero atoms	
7-19	p. 768
7-20	p. 769
7-21	p. 769
7-22	p. 770
7-23	p. 771
7-24	p. 771
C. Attack by nucleophiles on diazo compounds	
0-6	p. 306
0-19	p. 317
0-28	p. 324
0-48	p. 333
0-67	p. 345

Six-membered alicyclic rings may be aromatized in a number of ways.[6] Aromatization is accomplished most easily if there are already one or two double bonds in the ring or if the ring is fused to an aromatic ring. The reaction may also be applied to heterocyclic five- and six-membered rings. Many groups may be present on the ring without interference, and even *gem*-dialkyl substitution does not always prevent the reaction: in such cases one alkyl group often migrates or is eliminated. However, more drastic conditions are usually required for this. Seven-membered and larger rings are often isomerized to six-membered aromatic rings, though this is not the case for partially hydrogenated azulene systems (which are frequently found in nature): these are converted to azulenes.

There are two types of reagents most frequently used to effect aromatization. One group are hydrogenation catalysts such as platinum, palladium, nickel, etc. In this case the reaction is the reverse of double-bond hydrogenation (reactions **5-11** and **5-12**, pp. 591–599), and presumably the mechanism is also the reverse of that one, though not much is known. The other principal method is the use of sulfur or selenium, which combine with the hydrogen evolved to give H_2S or H_2Se. Little is known about this mechanism either.[7] Other reagents are sometimes used. Among these are atmospheric oxygen, SeO_2, quinones,[8] and activated charcoal.[9] The latter reagent can also dehydrogenate cyclopentanes to cyclopentadienes. The mechanism with quinones involves a transfer of hydride to the quinone oxygen, followed by the transfer of a proton to the phenolate ion:[8,10]

---

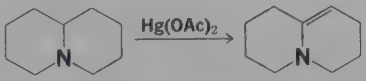
[6] For reviews, see Plattner, "Newer Methods of Preparative Organic Chemistry," vol. 1, pp. 21–59, Interscience Publishers, Inc., New York, 1948; and Valenta, in Bentley, "Elucidation of Structures by Physical and Chemical Methods" (vol. XI of Weissberger, "Technique of Organic Chemistry"), part 1, pp. 581–642, Interscience Publishers, Inc., New York, 1963.



In some instances the hydrogen is not released as H_2 or transferred to an external oxidizing agent, but instead serves to reduce another molecule of substrate. This is a disproportionation reaction and may be illustrated by the conversion of cyclohexene to cyclohexane and benzene.

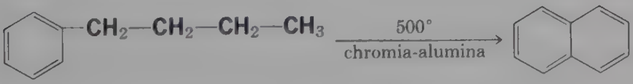
Aromatization reactions have been particularly important in the proof of structure of many cyclic natural products, especially steroids and terpenes. Diels-Alder adducts (which must contain at least one double bond) are also frequently aromatized.[11]

Dehydrogenation of open-chain systems to give a double bond in a specific location is not usually a feasible process, though industrially mixtures of olefins are obtained in this way from mixtures of alkanes. There are two notable exceptions: SeO_2 dehydrogenates 1,4-diones in good yield ($RCOCH_2CH_2COR \longrightarrow RCOCH{=}CHCOR$), and tertiary amines treated with mercuric acetate give enamines[12] in a synthesis developed by Leonard and coworkers.[13] For example,



OS **II,** 214, 423; **III,** 310, 729, 807; **IV,** 536. Also see OS **III,** 329, 358.

9-2 Cyclodehydrogenation



---

[7] House and Orchin, *J. Am. Chem. Soc.* **82,** 639 (1960); Silverwood and Orchin, *J. Org. Chem.* **27,** 3401 (1962).

[8] For a review, see Jackman, *Advan. Org. Chem.* **2,** 329–366 (1960).

[9] Shuikin and Naryschkina, *J. prakt. Chem.* [4] **13,** 183 (1961).

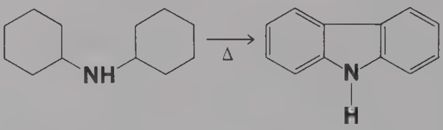
[10] Barnard and Jackman, *J. Chem. Soc.* **1960,** 3110; Braude, Jackman, Linstead, and Shannon, *J. Chem. Soc.* **1960,** 3116; Braude, Jackman, Linstead, and Lowe, *J. Chem. Soc.* **1960,** 3123, 3133.

[11] For a review of the aromatization of Diels-Alder adducts, see Skvarchenko, *Russ. Chem. Rev.* **32,** 571–589 (1963).

[12] For a review, see Szmuszkovicz, *Advan. Org. Chem.* **4,** 1–113 (1963), pp. 12–16.

[13] For example, see Leonard, Hay, Fulmer, and Gash, *J. Am. Chem. Soc.* **77,** 439 (1955); Leonard and Musker, *J. Am. Chem. Soc.* **81,** 5631 (1959), **82,** 5148 (1960); Leonard and Sauers, *J. Am. Chem. Soc.* **79,** 6210 (1957), *J. Org. Chem.* **21,** 1187 (1956).

Many aliphatic chains of at least six carbons have been pyrolyzed over chromia-alumina catalysts to yield aromatic compounds.[14] Where structural features permit (as in the reaction illustrated above), bicyclic and polycyclic compounds may be formed. Many heterocyclic aromatic compounds have also been made in this way. In some cases the chains are unsaturated and the only loss of hydrogen is from ring closure, but in other cases ring closure and aromatization (reaction **9-1**) take place concurrently. The majority of rings formed in this reaction are six-membered, but five-membered rings can also be formed, an example being[15]



The mechanism of these reactions is complex.[16]

9-3 Oxidation or dehydrogenation of alcohols to aldehydes and ketones

$$RCH_2OH \xrightarrow[\text{chromite}]{\text{copper}} RCHO$$

$$RCHOHR' \xrightarrow[H_2SO_4]{K_2Cr_2O_7} RCOR'$$

Primary alcohols may be converted to aldehydes, and secondary alcohols to ketones, in four main ways:

1. *With strong oxidizing agents.* Secondary alcohols are easily oxidized to ketones by acid dichromate, at room temperature or slightly above. Though this is the most common reagent, many other strong oxidizing agents (for example, $KMnO_4$, Br_2, MnO_2, etc.) have also been employed. For acid-sensitive compounds a CrO_3-pyridine complex may be used. These oxidizing agents have also been used to convert primary alcohols to aldehydes, but precautions must be taken so that the aldehyde is not further oxidized to the acid (reaction **9-20**). One way to halt oxidation is by evaporation of the aldehyde as it is formed. Lead tetraacetate in pyridine is a particularly mild reagent for these oxidations.[17]

2. *By catalytic dehydrogenation.*[18] For the conversion of primary alcohols

---

[14] For reviews, see Hansch, *Chem. Rev.* **53**, 353–396 (1953); and Pines and Goetschel, *J. Org. Chem.* **30**, 3530 (1965).

[15] Zelinskii, Titz, and Gaverdovskaya, *Ber.* **59**, 2590 (1926).

[16] For details, see Pines and Dembinski, *J. Org. Chem.* **30**, 3537 (1965); Pines, Goetschel, and Dembinski, *J. Org. Chem.* **30**, 3540 (1965); Goetschel and Pines, *J. Org. Chem.* **30**, 3544 (1965); Pines and Goetschel, *J. Org. Chem.* **30**, 3548 (1965).

[17] Partch, *Tetrahedron Letters* **1964**, 3071.

[18] For a review, see Heyns and Paulsen, in Foerst, "Newer Methods of Preparative Organic Chemistry," vol. 2, pp. 303–335, Academic Press Inc., New York, 1963 [also appears in *Angew. Chem.* **69**, 600 (1957)].

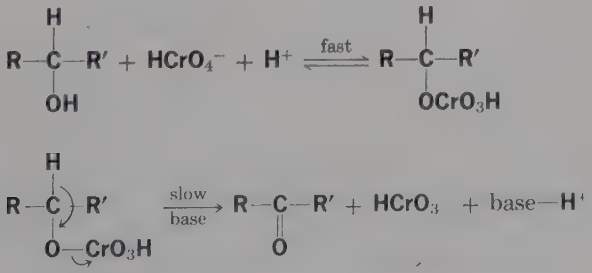
to aldehydes, dehydrogenation catalysts are usually preferred to strong oxidizing agents, because further oxidation to the acid is prevented. Copper chromite is the agent most often used, but other catalysts, e.g., silver and copper, have also been employed. Many ketones have also been prepared in this manner. The method is used for industrial preparation of several aldehydes and ketones.

3. *The Oppenauer oxidation.* When a ketone in the presence of base is used as the oxidizing agent (it is reduced to a secondary alcohol), the reaction is known as the *Oppenauer oxidation.*[19] This is the reverse of the Meerwein-Ponndorf-Verley reaction (**6-27**, p. 678), and the mechanism is also the reverse. The ketones most commonly used are acetone, methyl ethyl ketone, and cyclohexanone. The most common base is potassium *tert*-butoxide. The chief advantage of the method is its high selectivity. Though the method is most often used for the preparation of ketones, it has also been used to prepare aldehydes.

4. *With* N-*bromosuccinimide or related compounds.* These compounds are selective oxidizing agents and often oxidize OH groups without disturbing other oxidizable groups.[20] N-Bromosuccinimide does not oxidize aliphatic primary alcohols, but N-chlorosuccinimide does. The mechanism is not clear. The reactions readily proceed in the dark, so that the mechanism is probably not of the free-radical type, but involves attack by positive bromine.

Primary and secondary alcohols may also be oxidized, indirectly, through their esters (see reaction **9-19**). In some cases, isolation of the ester is not required, and the alcohol may then be oxidized to the aldehyde or ketone in one step. Benzyl alcohols may be oxidized to aldehydes with cerium(IV).[20a]

The mechanism of oxidation with acid dichromate has been intensively studied.[21] Westheimer[22] proposed a mechanism which is an example of category 4 (p. 856):



1. $$R-\overset{H}{\underset{OH}{C}}-R' + HCrO_4^- + H^+ \xrightleftharpoons{\text{fast}} R-\overset{H}{\underset{OCrO_3H}{C}}-R'$$

2. $$R-\overset{H}{\underset{O-CrO_3H}{C}}-R' \xrightarrow[\text{base}]{\text{slow}} R-\underset{\overset{\|}{O}}{C}-R' + HCrO_3 + \text{base}-H^+$$

[19] For reviews, see Djerassi, *Org. Reactions* **6**, 207–272 (1951); Bersin, "Newer Methods of Preparative Organic Chemistry," vol. 1, pp. 125–158, 143–158, Interscience Publishers, Inc., New York, 1948.

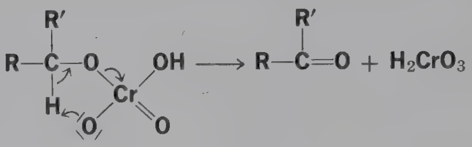
[20] For a review, see Filler, *Chem. Rev.* **63**, 21–43 (1963), pp. 22–28.

[20a] Trahanovsky and Young, *J. Chem. Soc.* **1965**, 5777.

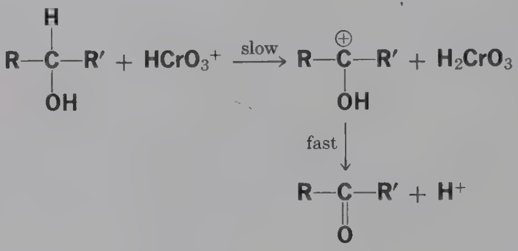
[21] For reviews, see Venkatasubramanian, *J. Sci. Ind. Res.* (*India*) **22**, 397–400 (1963); Waters, Ref. 1, pp. 49–71; and Stewart, Ref. 1, pp. 37–48.

[22] Westheimer, *Chem. Rev.* **45**, 419–451 (1949), p. 434; Holloway, Cohen, and Westheimer, *J. Am. Chem. Soc.* **73**, 65 (1951).

In most cases the base is water. Part of the evidence for this mechanism was the isotope effect of about 6 found upon use of MeCDOHMe, showing that the α hydrogen is removed in the rate-determining step.[23] This mechanism was modified by Kwart and Francis.[24] In their proposal, the first step is the same, but in the second step the base is not external but is one of the oxygens on the chromium, so that the transition state is cyclic:[25]



However, it has been shown that electron-donating substituents increase the rate of the reaction, which is not what would be predicted by removal of the hydrogen as a proton.[24,26] Accordingly, a mechanism was suggested in which the hydrogen is lost as hydride ion:[27]



$$\mathrm{R{-}\overset{H}{\underset{OH}{C}}{-}R'} + \mathrm{HCrO_3^+} \xrightarrow{\text{slow}} \mathrm{R{-}\overset{\oplus}{\underset{OH}{C}}{-}R'} + \mathrm{H_2CrO_3} \xrightarrow{\text{fast}} \mathrm{R{-}\underset{O}{\underset{\|}{C}}{-}R'} + \mathrm{H^+}$$

This mechanism is also compatible with the observed isotope effect. An important piece of evidence for the ester mechanism (whether cyclic or not) was the finding that diisopropyl ether, which could be oxidized to acetone by the hydride mechanism, but not by the ester mechanism, was oxidized $\frac{1}{1500}$ as fast as isopropyl alcohol.[28] Further evidence for the ester mechanism is that, with alcohols containing sterically hindered OH groups, step 1 (involving no cleavage of the C—H bond) could be made rate-determining.[29] This is hardly compatible with the hydride mechanism. On balance then, it seems that the ester mechanism is the most likely one when the oxidizing agent is acid dichromate. With other oxidizing agents, mechanisms are less clear. It seems certain that some oxidizing agents operate by a hydride-shift mechanism, for example, dehydrogenation with triphenylmethyl cation[30] and the Oppenauer oxidation, and some by a free-radical mechanism, for example, oxidation with $S_2O_8^{=}$[31] and with VO_2^+.[32] A summary of many proposed mechanisms is given by Littler.[33] For the oxidation of cyclohexanol by bromine, a cyclic mechanism has been proposed:[34]

---

[23] Westheimer and Nicolaides, *J. Am. Chem. Soc.* **71**, 25 (1949).

[24] Kwart and Francis, *J. Am. Chem. Soc.* **81**, 2116 (1959).

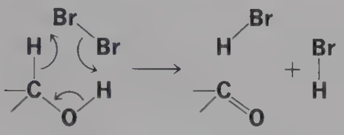
[25] This cyclic mechanism has been supported by Stewart and Lee, *Can. J. Chem.* **42**, 439 (1964).

[26] Venkatasubramanian, *Indian J. Chem.* **1**, 48 (1963).

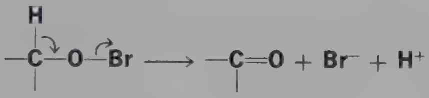
[27] Roček and Krupicka, *Chem. Ind.* (*London*) **1957**, 1668; *Collection Czech. Chem. Commun.* **23**, 2068 (1958).

[28] Brownell, Leo, Chang, and Westheimer, *J. Am. Chem. Soc.* **82**, 406 (1960).

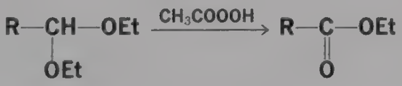
[29] Roček, Westheimer, Eschenmoser, Moldoványi, and Schreiber, *Helv. Chim. Acta* **45**, 2554 (1962).



though it is possible to envision this as proceeding through a hypohalite intermediate:



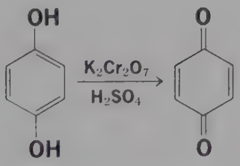
Acetals may be oxidized to esters with peracetic acid:[35]



$$R{-}\underset{\substack{|\\ OEt}}{CH}{-}OEt \xrightarrow{CH_3COOOH} R{-}\underset{\substack{\|\\ O}}{C}{-}OEt$$

OS **I,** 87, 211, 241, 340; **II,** 139, 541; **III,** 37, 207; **IV,** 189, 192, 195, 467, 813, 838; **42,** 36, 79; **45,** 28, 57, 77. Also see OS **IV,** 283.

9-4 Oxidation of phenols and aromatic amines to quinones



Ortho and para diols are easily oxidized to *ortho*- and *para*-quinones, respectively.[36] Either or both OH groups may be replaced by NH_2 groups to give the same products, though for the preparation of *ortho*-quinones only OH groups are normally satisfactory. When NH_2 groups are present, then the intermediate is an imine (for example **1**, from *p*-phenylenediamine), which, under the reaction conditions, is hydrolyzed to the quinone. The reaction has been successfully carried out with other groups para to OH or NH_2: halogen, OR, Me, and even H, though with the latter yields are poor. Many oxidizing agents have been used: acid dichromate, lead tetraacetate, HIO_4, and atmospheric oxygen, to name a few. The reaction is not exactly analogous to reaction **9-3**, which is an elimination to form a C=O bond. This reaction may be looked upon as a 1,6 elimination of two hydrogens.

---

[30] Bonthrone and Reid, *J. Chem. Soc.* **1959,** 2773.

[31] Ball, Crutchfield, and Edwards, *J. Org. Chem.* **25,** 1599 (1960).

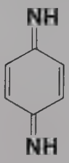
[32] Littler and Waters, *J. Chem. Soc.* **1959,** 4046.

[33] Littler, *J. Chem. Soc.* **1962,** 2190.

[34] Barker, Overend, and Rees, *J. Chem. Soc.* **1964,** 3263.

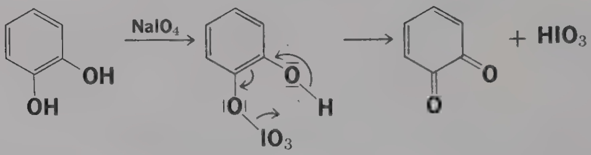
[35] Heywood and Phillips, *J. Org. Chem.* **25,** 1699 (1960).

[36] For a review, see Cason, *Org. Reactions* **4,** 305–361 (1948).



1

Less is known about the mechanism than is the case for reaction **9-3**, but, as in that case, it seems to vary with the oxidizing agent. For oxidation of catechol with $NaIO_4$, it was found that the reaction conducted in $H_2{}^{18}O$ gave unlabeled quinone,[37] so that the following mechanism, which is an example of category 4 (p. 856), was proposed:



However, for autoxidations (i.e., with atmospheric oxygen) a free-radical mechanism is known to operate.[38]

OS **I**, 383, 482, 511; **II**, 175, 254, 430, 553; **III**, 633, 753; **IV**, 148.

9-5 Dehydrogenation of amines

$$RCH_2NH_2 \xrightarrow[2.\ H_2O]{1.\ IF_5} RCN$$

Primary amines at a primary carbon can be dehydrogenated to nitriles. The reaction has been carried out in a variety of ways: by treatment with IF_5,[39] NaOBr, or lead tetraacetate,[40] as well as catalytically.[41] Secondary amines can sometimes be dehydrogenated to imines.[42] Primary alcohols or aldehydes can be converted directly to nitriles by air oxidation in the presence of ammonia, a strong base (such as OMe^-) and a copper complex.[43] This reaction is a combination of three reactions: oxidation of the alcohol to the aldehyde (reaction **9-3**), formation of the imine (reaction **6-14**, p. 666), and dehydrogenation of this to the nitrile.

---

[37] Adler, Falkehag, and Smith, *Acta Chem. Scand.* **16**, 529 (1962).

[38] Walling, "Free Radicals in Solution," pp. 457–461, John Wiley & Sons, Inc., New York, 1957.

[39] Stevens, *J. Org. Chem.* **26**, 2531 (1961).

[40] Mihailović, Stojiljković, and Andrejević, *Tetrahedron Letters* **1965**, 461.

[41] Peters, Marple, Evans, McAllister, and Castner, *Ind. Eng. Chem.* **40**, 2046 (1948).

[42] Henbest and Slade, *J. Chem. Soc.* **1960**, 1558; Shechter and Rawalay, *J. Am. Chem. Soc.* **86**, 1706 (1964).

[43] Brackman and Smit, *Rec. trav. chim.* **82**, 757 (1963).

9-6 Oxidation of hydrazines

$$\mathrm{Ar{-}NH{-}NH{-}Ar} \xrightarrow{\mathrm{NaOBr}} \mathrm{Ar{-}N{=}N{-}Ar}$$

N,N′-Diarylhydrazines (hydrazo compounds) are oxidized to azo compounds by several oxidizing agents, including NaOBr, $CuCl_2$, and air and NaOH. The reaction is also applicable to N,N′-dialkylhydrazines. Hydrazines (both alkyl and aryl) substituted on only one side also give azo compounds, but these are unstable and decompose to give nitrogen and the hydrocarbon:

$$\mathrm{Ar{-}NH{-}NH_2} \longrightarrow [\mathrm{Ar{-}N{=}NH}] \longrightarrow \mathrm{ArH} + \mathrm{N_2}$$

When hydrazones are oxidized with mercuric oxide, diazo compounds are obtained:

$$\mathrm{R_2C{=}N{-}NH_2} \xrightarrow{\mathrm{HgO}} \mathrm{R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N}}$$

Diazo ketones have been prepared from glyoxal monohydrazones by oxidation with MnO_2:[44]

$$\mathrm{Ar{-}CO{-}C{=}N{-}NH_2} + \mathrm{MnO_2} \longrightarrow \mathrm{Ar{-}CO{-}CN_2}$$

The glyoxal monohydrazones were synthesized by treatment of phenacyl bromides ($ArCOCH_2Br$) with hydrazine.[44]

OS **II**, 496; **III**, 351, 356, 375; **IV**, 66, 411; **44**, 18; **45**, 83.

9-7 Oxidation of hydroxylamines

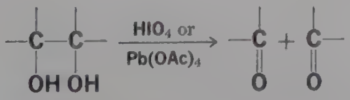
$$\mathrm{Ar{-}NH{-}OH} \xrightarrow{\mathrm{CrO_3}} \mathrm{Ar{-}N{=}O}$$

Aromatic hydroxylamines are easily oxidized to nitroso compounds, most commonly by acid dichromate.

OS **III**, 668.

B. Oxidations involving cleavage of carbon-carbon bonds

9-8 Oxidative cleavage of glycols and related compounds



$$\mathrm{-\underset{OH}{\overset{|}{\underset{|}{C}}}-\underset{OH}{\overset{|}{\underset{|}{C}}}-} \xrightarrow[\mathrm{Pb(OAc)_4}]{\mathrm{HIO_4\ or}} \mathrm{-\underset{O}{\underset{\|}{\overset{|}{C}}}} + \mathrm{\underset{O}{\underset{\|}{\overset{|}{C}}}-}$$

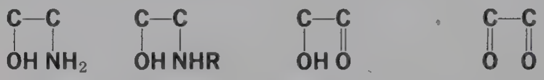
---

[44] Hauptmann, Kluge, Seidig, and Wilde, *Angew. Chem. Intern. Ed. Engl.* **4**, 688 (1965).

1,2-Glycols are easily cleaved, under mild conditions, and in good yield, with periodic acid or lead tetraacetate.[45] The products are two moles of aldehyde or two of ketone, or one of each, depending on the groups attached to the two carbons. The yields are so good that olefins are often converted to glycols (reaction **5-28**, p. 616) and then cleaved with HIO_4 or $Pb(OAc)_4$ rather than being cleaved directly with ozone (reaction **9-10**) or dichromate or permanganate (reaction **9-11**). Permanganate and dichromate also cleave glycols, giving carboxylic acids rather than aldehydes, but these reagents are seldom used synthetically.

The two reagents (periodic acid and lead tetraacetate) are complementary, since periodic acid is best used in water, and lead tetraacetate in organic solvents. When three or more OH groups are located on adjacent carbons, then the middle one (or ones) is converted to formic acid. This reaction is used a great deal in carbohydrate chemistry, more for structure identification than for preparative purposes.

Similar cleavage is undergone by other compounds which contain oxygens or nitrogens on adjacent carbons:



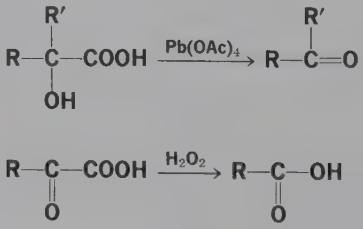
$$\underset{OH}{\underset{|}{C}}-\underset{NH_2}{\underset{|}{C}} \qquad \underset{OH}{\underset{|}{C}}-\underset{NHR}{\underset{|}{C}} \qquad \underset{OH}{\underset{|}{C}}-\underset{O}{\underset{\|}{C}} \qquad \underset{O}{\underset{\|}{C}}-\underset{O}{\underset{\|}{C}}$$

β-Amino alcohols

α-Hydroxy aldehydes and ketones

α-Diketones
α-Keto aldehydes
Glyoxal

α-Diketones are also cleaved by alkaline H_2O_2, to give two molecules of carboxylic acid. α-Hydroxy acids and α-keto acids are not cleaved by HIO_4 but are cleaved by $Pb(OAc)_4$, alkaline H_2O_2, and other reagents. These are oxidative decarboxylations. α-Hydroxy acids give aldehydes or ketones, and α-keto acids give acids:



$$R-\overset{R'}{\overset{|}{\underset{OH}{\underset{|}{C}}}}-COOH \xrightarrow{Pb(OAc)_4} R-\overset{R'}{\overset{|}{C}}=O$$

$$R-\underset{O}{\underset{\|}{C}}-COOH \xrightarrow{H_2O_2} R-\underset{O}{\underset{\|}{C}}-OH$$

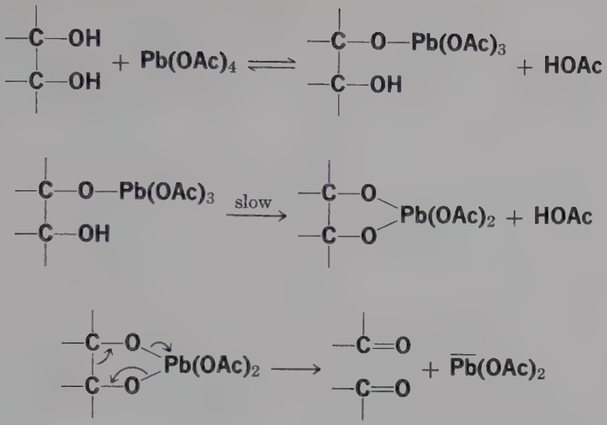
Also see reaction **0-13** (p. 315).

The mechanism of glycol oxidation with $Pb(OAc)_4$ was proposed by Criegee:[46]

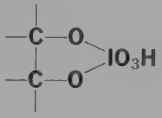
---

[45] For a review covering HIO_4, see Jackson, *Org. Reactions* **2**, 341–375 (1944). For reviews covering both reagents, see Bunton, in Wiberg, "Oxidation in Organic Chemistry," vol. 1, pp. 367–407, Academic Press Inc., New York, 1965; and Criegee, in "Newer Methods of Preparative Organic Chemistry," vol. 1, pp. 12–20, Interscience Publishers, Inc., New York, 1948.

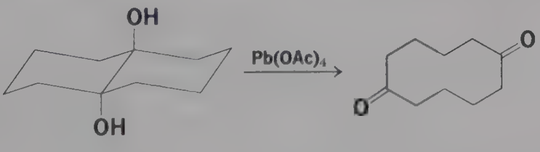
[46] Criegee, Kraft, and Rank, *Ann.* **507**, 159 (1933). For reviews, see Wasserman, in Newman, "Steric Effects in Organic Chemistry," pp. 378–387, John Wiley & Sons, Inc., New York, 1956; Waters, Ref. 1, pp. 72–81; Stewart, Ref. 1, pp. 97–106.



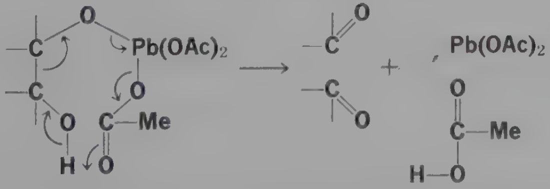
This mechanism is supported by (1) second-order kinetics (first order in each reactant); (2) added acetic acid retards the reaction (drives the equilibrium to the left); and (3) cis glycols react much more rapidly than trans glycols.[47] For periodic acid the mechanism is similar, with the intermediate:[48]



However, the cyclic-intermediate mechanism cannot account for all glycol oxidations, since some glycols which cannot form such an ester (for example, **2**) are nevertheless cleaved (though other glycols which cannot form cyclic esters are *not* cleaved, by either reagent[49]). To account for cases like **2**, a cyclic transition state has been proposed:[47]



2



---

[47] For example, see Criegee, Höger, Huber, Kruck, Marktscheffel, and Schellenberger, *Ann.* **599**, 81 (1956).

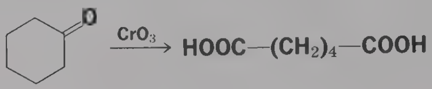
[48] Buist, Bunton, and Miles, *J. Chem. Soc.* **1959**, 743.

[49] Angyal and Young, *J. Am. Chem. Soc.* **81**, 5251 (1959).

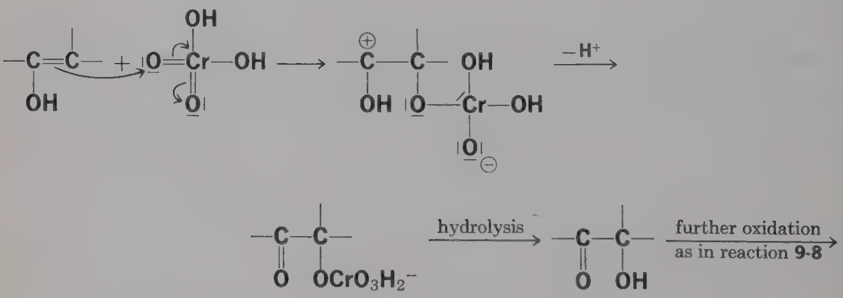
Oxidation by strong oxidizing agents (for example, CrO_3) is probably also through a cyclic intermediate, at least for open-chain and cis cyclic diols,[50] though with some reagents a free-radical mechanism has been demonstrated.[51]

OS **IV**, 124.

9-9 Oxidative cleavage of ketones and alcohols



Oxidative cleavage of open-chain ketones or alcohols is seldom a useful preparative procedure, not because these compounds do not undergo oxidation (they do, with the exception of diaryl ketones) but because the result is generally a hopeless mixture. However, the reaction is quite useful for cyclic ketones and the corresponding secondary alcohols, the dicarboxylic acid being prepared in good yield. Acid dichromate and permanganate are the most common oxidizing agents, though autoxidation (oxidation with atmospheric oxygen) in alkaline solution has also been used.[52] The mechanism with strong oxidizing agents is probably through the enol form of the ketone (in the case of alcohols, oxidation to the ketone is a preliminary step).[53] The process may be illustrated for chromic acid:



The formation of the chromium ester from the enol is similar to the bromination of ketones (reaction **2-4**, p. 458). A similar mechanism was demonstrated for nitric acid.[54] However, in some cases, the ketone is attacked directly, and not through the enol.[55]

Cyclic ketones may also be cleaved in other ways. Photolytic cleavage[56] gives mono acids, e.g.,

---

[50] Roček and Westheimer, *J. Am. Chem. Soc.* **84**, 2241 (1962); Kwart, Ford, and Corey, *J. Am. Chem. Soc.* **84**, 1252 (1962).

[51] Littler, Mallet, and Waters, *J. Chem. Soc.* **1960**, 2761.

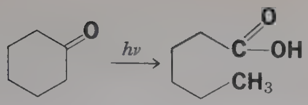
[52] Wallace, Pobiner, and Schriesheim, *J. Org. Chem.* **30**, 3768 (1965).

[53] Best, Littler, and Waters, *J. Chem. Soc.* **1962**, 822; Littler, *J. Chem. Soc.* **1962**, 827, 833.

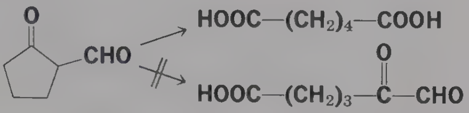
[54] van Asselt and van Krevelen, *Rec. trav. chim.* **82**, 51 (1963).

[55] Littler, *J. Chem. Soc.* **1962**, 833.

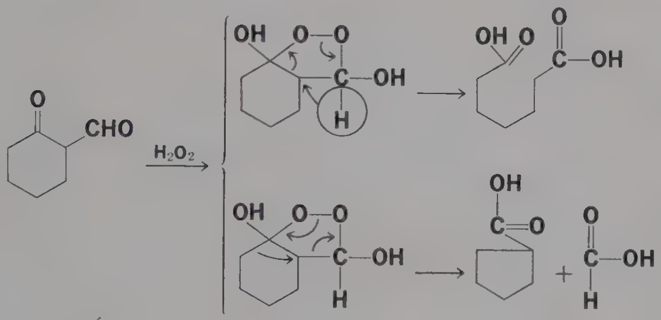
[56] For a review, see Quinkert, *Angew. Chem. Intern. Ed. Engl.* **4**, 211–222 (1965).



2-Formylcycloalkanones are cleaved with H_2O_2, but the expected product is not obtained:[57]

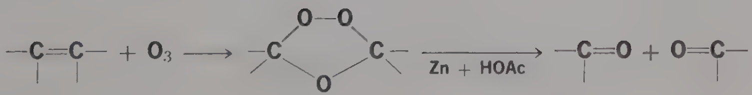


This is a rearrangement, and ring contraction is a side reaction, e.g.,



OS **I,** 18; **IV,** 19.

9-10 Ozonolysis



3

When compounds containing double bonds are treated with ozone, they are converted to compounds called ozonides (**3**), which can be isolated but are more often decomposed with zinc and acetic acid or catalytic hydrogenation to give two moles of aldehyde, or two of ketone, or one of each, depending on the groups attached to the olefin.[58] High yields of aldehydes can be obtained by treatment of the ozonolysis mixture with dimethyl sulfide.[58a] However, ozonides may also be *oxidized* with oxygen or H_2O_2, to give ketones and/or carboxylic acids, or *reduced* with $LiAlH_4$ or $NaBH_4$, to give two moles of alcohol.[59] Ozonides may also be treated with ammonia, hydrogen, and a catalyst to give the corresponding amines.[60] Ozonolysis has been very valuable for location of the double bonds in unknown compounds, though with the advent of instrumental methods of structure determination, this usage has declined.

---

[57] Zavialov, Vinogradova, and Kondratieva, *Tetrahedron* **20,** 2745 (1964).

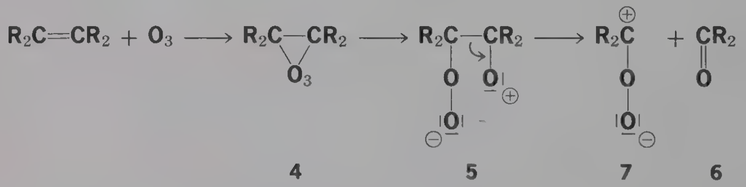
[58] For a review, see Bailey, *Chem. Rev.* **58,** 925–1010 (1958).

[58a] Pappas, Keaveney, Gancher, and Berger, *Tetrahedron Letters* **1966,** 4273.

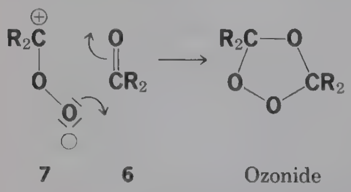
[59] Sousa and Bluhm, *J. Org. Chem.* **25,** 108 (1960); Diaper and Mitchell, *Can. J. Chem.* **38,** 1976 (1960).

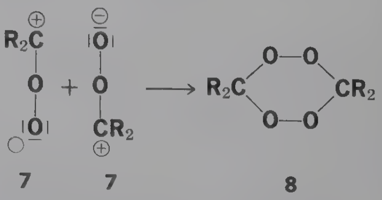
A wide variety of olefins undergo ozonolysis, including cyclic ones, where cleavage gives rise to one bifunctional product. The reaction has often been carried out on compounds containing more than one double bond: generally the bonds are all cleaved. Ozonolysis of triple bonds is less common and the reaction proceeds less easily, since ozone is an electrophilic agent and therefore prefers double to triple bonds (p. 575). Compounds which contain triple bonds generally give acids, though sometimes ozone oxidizes them to α-diketones. Acetylenic ethers give α-keto esters:[61] $RC{\equiv}COR' \longrightarrow RCOCOOR'$. Aromatic compounds are also attacked less readily than olefins, but they have often been cleaved. Aromatic compounds behave as if the double bonds in the Kekulé structures were really there. Thus benzene gives three moles of glyoxal (HCOCHO), and *o*-xylene gives products in the ratio 3glyoxal : 2MeCOCHO : 1MeCOCOMe, which shows that in this case cleavage is statistical. With polycyclic aromatic compounds the site of attack depends on the structure of the molecule and on the solvent.[62]

Although a large amount of work has been done on the mechanism of ozonization (formation of **3**), not all the details are known. The knowledge we do have about the mechanism is largely due to Criegee.[63] The first step is addition of ozone to the olefin to give an "initial ozonide" (**4**) in which there is still a bond between the two carbons. Criegee did not specify the structure of this species, but it is unstable and breaks apart to give the zwitterion **5**, which then cleaves into an aldehyde or ketone (**6**) and a different zwitterion (**7**):



7 may then undergo various reactions, two of which lead to normal products. One of these is a recombination with **6**, and the other is a dimerization to the bisperoxide **8**:





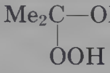
---

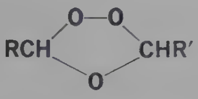
[60] Diaper and Mitchell, *Can. J. Chem.* **40,** 1189 (1962); Benton and Kiess, *J. Org. Chem.* **25,** 470 (1960); Pollart and Miller, *J. Org. Chem.* **27,** 2392 (1962).

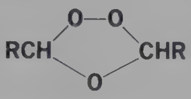
[61] Wisaksono and Arens, *Rec. trav. chim.* **80,** 846 (1961).

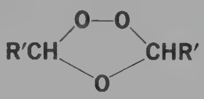
[62] Dobinson and Bailey, *Tetrahedron Letters* **1960,** Nos. 13, 14.

[63] For a review, see Criegee, *Record Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) **18,** 111 (1957).

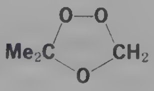
If the first path is taken, then hydrolysis of the ozonide gives the normal products. If **8** is formed, then hydrolysis of it gives one of the products, and, of course, **6**, which does not then undergo further reaction, is the other. In protic solvents, **7** is converted to a hydroperoxide, and these have been isolated, for example,  $\underset{\mathrm{OOH}}{\mathrm{Me_2C}}\text{—OMe}$ from $Me_2C{=}CMe_2$ in methanol. Further evidence for the mechanism is that **8** can be isolated in some cases, e.g., from $Me_2C{=}CMe_2$. But perhaps the most impressive evidence comes from the detection of cross products. In this mechanism, the two parts of the original olefin break apart and then recombine to form the ozonide. In the case of an unsymmetrical olefin RCH=CHR′ there should then be three ozonides:







since there will be two different aldehydes **6** and two different zwitterions **7**, and these can recombine in the three ways shown. Actually *six* ozonides, corresponding to the cis and trans forms of these three, were isolated and characterized for methyl oleate.[64] Similar results have been reported for smaller olefins, e.g., 2-pentene, 2-hexene, 4-nonene, and even 2-methyl-2-pentene.[65] The latter case is especially interesting, since it is quite plausible that this very unsymmetrical olefin would cleave in only one way, so that only one ozonide (in cis and trans versions) would be found; but this is not so, and three were found for this case too. In general, the less alkylated end of the olefin tends to go to **6** and the other to **7**. Still other evidence for the Criegee mechanism is that, when $Me_2C{=}CMe_2$ was ozonized in the presence of HCHO, then the ozonide **9** could be isolated, and that cis and trans olefins generally give the same ozonide, which would be expected if they cleave first. However, this was not true for $Me_3CCH{=}CHCMe_3$, where the cis olefin gave the cis ozonide (chiefly), and the trans gave the trans.[66] The latter result is not compatible with the Criegee mechanism, and it is possible that other mechanisms also operate. Support for this view was offered by the finding that the cis-trans ratios of symmetrical (cross) ozonides obtained from *cis*- and *trans*-4-methyl-2-pentene were not the same:[66a]



9

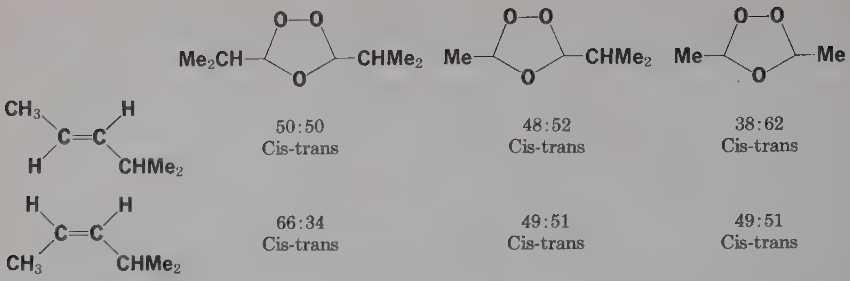
---

[64] Riezebos, Grimmelikhuysen, and van Dorp, *Rec. trav. chim.* **82**, 1234 (1963); Privett and Nickell, *J. Am. Oil Chemists Soc.* **41**, 72 (1964).

[65] Loan, Murray, and Story, *J. Am. Chem. Soc.* **87**, 737 (1965); Lorenz and Parks, *J. Org. Chem.* **30**, 1976 (1965).

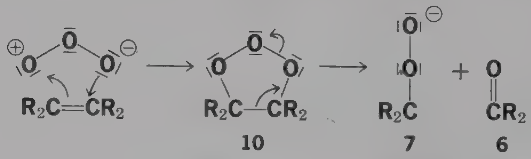
[66] Schröder, *Chem. Ber.* **95**, 733 (1962).

[66a] Murray, Youssefyeh, and Story, *J., Am. Chem. Soc.* **88**, 3143, 3655 (1966); Story, Murray, and Youssefyeh, *J. Am. Chem. Soc.* **88**, 3144 (1966). Also see Greenwood, *J. Am. Chem. Soc.* **88**, 3146 (1966).

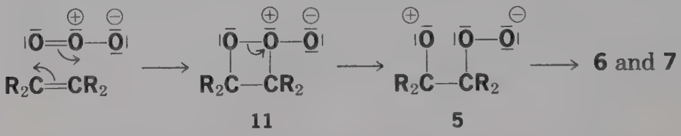


If the Criegee mechanism were the only one, the cis-trans ratio for each of the two cross ozonides would have to be identical for the cis and trans olefins, since in this mechanism they are completely cleaved.

Two main possibilities have been proposed for the structure of the initial ozonide **4**. The ozone may add to the olefin in a 1,3-dipolar addition (see reaction **5-33**, p. 623), in which case the initial ozonide would be **10**:



In this case **5** would not be an intermediate. The other possibility is closing of a four-membered ring, involving the intermediate **11**:



The intermediate **11** was first proposed by Staudinger,[67] who gave it the name *molozonide*. The structure of the intermediate has been determined in only one case, that of *trans*-$Me_3CCH{=}CHCMe_3$. A crystalline material isolated at low temperatures was found by nmr to have the structure **10**,[68] showing that at least in this case the initial reaction is 1,3-dipolar addition. The compound gave the ozonide on warming. No such solid could be isolated from the cis isomer. However, both *cis*- and *trans*-3-hexene did give corresponding white solids at −112°.[69]

A similar mechanism is likely for the reaction of triple bonds with ozone.[70] Less is known about how ozonides are converted to products.

OS **41,** 41, 46. Also see OS **IV,** 554. For the preparation of ozone, see OS **III,** 673.

[67] Staudinger, *Ber.* **58,** 1088 (1925).

[68] The isolation was first reported by Criegee and Schröder, *Chem. Ber.* **93,** 689 (1960). The structure was established by Bailey, Thompson, and Shoulders, *J. Am. Chem. Soc.* **88,** 4098 (1966). See also Durham and Greenwood, *Chem. Commun.* **1967,** 843.

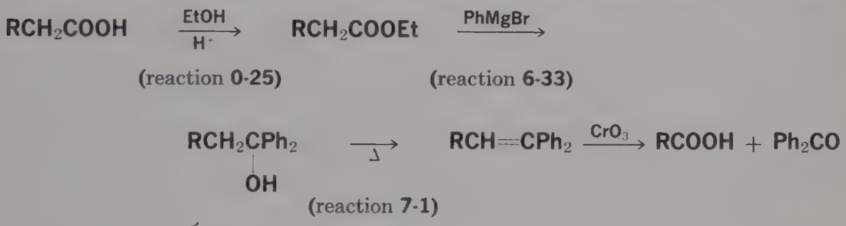
[69] Greenwood, *J. Org. Chem.* **29,** 1321 (1964); Greenwood and Haske, *Tetrahedron Letters* **1965,** 631.

[70] Bailey, Chang, and Kwie, *J. Org. Chem.* **27,** 1198 (1962).

9-11 Oxidative cleavage of double bonds

$$R_2C{=}CHR \xrightarrow{CrO_3} R_2C{=}O + RCOOH$$

Double bonds may be cleaved by many oxidizing agents, the most common of which are neutral or acid permanganate and acid dichromate. The products are generally two moles of ketone, two moles of carboxylic acid, or a mole of each, depending on what groups are attached to the olefin. Sometimes the reaction can be stopped at the aldehyde stage. For example, cyclic olefins are oxidized to dialdehydes by chromyl trichloroacetate, $O_2Cr(OCOCCl_3)_2$.[71] However, the oxidative cleavage of double bonds is not usually a useful method for preparative purposes. When the reaction *is* desired for preparative purposes, the most common reagent is a solution of HIO_4 containing a trace of MnO_4^-.[72] The *Barbier-Wieland procedure* for decreasing the length of a chain by one carbon involves oxidative cleavage, but this is cleavage of a 1,1-diphenyl olefin, which generally gives good yields:



$$RCH_2COOH \xrightarrow[H^+]{EtOH} RCH_2COOEt \xrightarrow{PhMgBr}$$

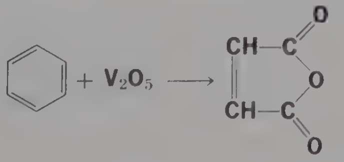
(reaction **0-25**) (reaction **6-33**)

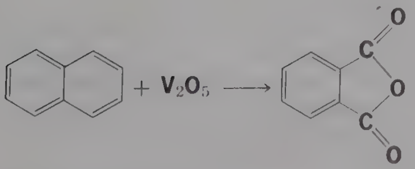
$$\underset{\textstyle OH}{RCH_2CPh_2} \xrightarrow[\Delta]{} RCH{=}CPh_2 \xrightarrow{CrO_3} RCOOH + Ph_2CO$$

(reaction **7-1**)

The mechanism of oxidation probably involves in most cases the initial formation of a glycol (reaction **5-28**, p. 616) or at least a cyclic ester, and then a further oxidation as in reaction **9-8**. In line with the electrophilic attack on the olefin, triple bonds are more resistant to oxidation than double bonds.

Aromatic rings may be cleaved with strong enough oxidizing agents. The most common example is oxidation of benzene and naphthalene with V_2O_5:



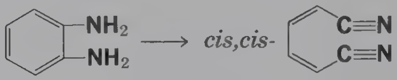


---

[71] Schildknecht and Föttinger, *Ann.* **659**, 20 (1962).

[72] Lemieux and Rudloff, *Can. J. Chem.* **33**, 1701, 1710 (1955); Rudloff, *Can. J. Chem.* **33**, 1714 (1955), **34**, 1413 (1956), **43**, 1784 (1965).

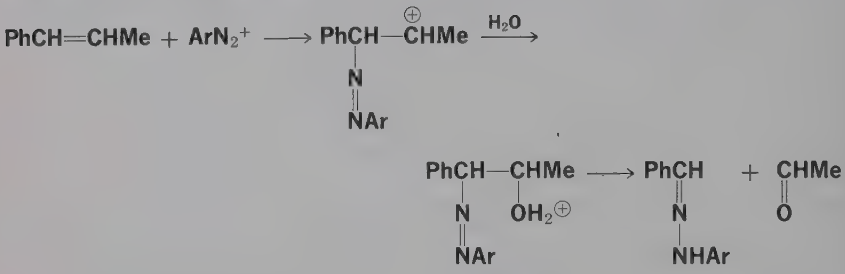
These are important industrial procedures. *o*-Diamines have been oxidized with nickel peroxide and with lead tetraacetate:[73]



Double bonds may be cleaved in other ways. Treatment with NH_2NH^- gives a hydrazone:[74]

$$R_2C{=}CR_2 + NH_2NH^- \longrightarrow R_2CH_2 + R_2C{=}NNH_2$$

Certain olefins may be cleaved with diazonium salts to give aldehydes or ketones and arylhydrazones:[75]



$$PhCH{=}CHMe + ArN_2^+ \longrightarrow \underset{\begin{array}{c}|\\N\\\|\\NAr\end{array}}{PhCH}-\overset{\oplus}{C}HMe \xrightarrow{H_2O}$$

$$\underset{\begin{array}{c}|\\N\\\|\\NAr\end{array}}{PhCH}-\underset{\begin{array}{c}|\\OH_2^{\oplus}\end{array}}{CHMe} \longrightarrow \underset{\begin{array}{c}\|\\N\\|\\NHAr\end{array}}{PhCH} + \underset{\begin{array}{c}\|\\O\end{array}}{CHMe}$$

OS **II,** 53, 523; **III,** 39, 234, 449; **IV,** 136, 484, 824; **42,** 44. Also see OS **II,** 551.

9-12 Oxidation of aromatic side chains

$$ArR \xrightarrow{KMnO_4} ArCOOH$$

Alkyl side chains on aromatic rings may be oxidized to COOH groups by many oxidizing agents, including permanganate and acid dichromate. The method is most often applied to the methyl group, though longer side chains can also be cleaved. However, tertiary alkyl groups are resistant to oxidation, and when they *are* oxidized, ring cleavage usually occurs too.[76] It is usually difficult to oxidize an R group on a fused aromatic system without cleaving the ring. However, this has been done (e.g., 2-methylnaphthalene was converted to naphthoic acid) with aqueous $Na_2Cr_2O_7$.[77] Functional groups may be present anywhere on the side chain and, if in the α position, greatly increase the ease of oxidation. However, an exception is an α-phenyl group. In such cases the reaction stops at the diaryl ketone stage. Molecules containing aryl groups on different carbons cleave so that each ring gets one carbon atom, e.g.,

---

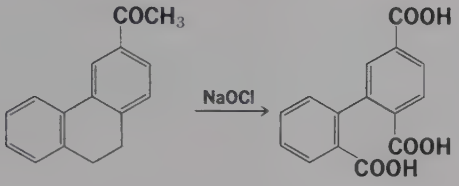
[73] Nakagawa and Onoue, *Tetrahedron Letters* **1965**, 1433, *Chem. Commun.* **1966**, 396.

[74] Kauffmann, Henkler, Kosel, Rauch, Schultz, and Weber, *Angew. Chem. Intern. Ed. Engl.* **1**, 456 (1962).

[75] Marxmeier and Pfeil, *Ann.* **678**, 28 (1964), *Chem. Ber.* **97**, 815 (1964).

[76] Brandenberger, Maas, and Dvoretsky, *J. Am. Chem. Soc.* **83**, 2146 (1961).

[77] Friedman, Fishel, and Shechter, *J. Org. Chem.* **30**, 1453 (1965).

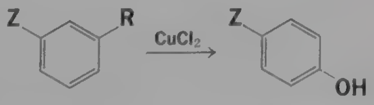


It is possible to oxidize only one alkyl group of a ring that contains more than one. Groups on the ring which are susceptible to oxidation (OH, NHR, NH_2, etc.) must be protected. The oxidation may be performed with oxygen, in which case it is autoxidation, and the mechanism is like that in reaction **4-8** (p. 543), with a hydroperoxide intermediate. With this procedure it is possible to isolate ketones from $ArCH_2R$.

The mechanism has been studied for the closely related reaction: $Ar_2CH_2 + CrO_3 \longrightarrow Ar_2C{=}O$.[78] An isotope effect of 6.4 was found, indicating that the rate-determining step is either $Ar_2CH_2 \longrightarrow Ar_2CH\cdot$ or $Ar_2CH_2 \longrightarrow Ar_2CH^+$. Either way this explains why tertiary groups are not converted to COOH and why the order of reactivity for other groups is $CH_2Ar > CHR_2 > CH_2R > CH_3$.[79] Both free radicals and carbonium ions exhibit this order of stability (Chapter 5). The two possibilities are examples of categories 2 and 3 (p. 855). Just how the free radical or carbonium ion goes on to the product is not known. $\mathrm{Ar{-}\overset{|}{\underset{|}{C}}{-}OH}$ may be an intermediate, in which case the further reaction would be like that in reaction **9-3.**

OS **I,** 159, 385, 392, 543; **II,** 135, 428; **III,** 334, 420, 740, 791, 820, 822; **40,** 48; **43,** 80.

9-13 Oxidative cleavage of alkyl groups from rings



It is possible to replace an alkyl group on a ring by an OH group. When the alkyl group is one oxidizable to COOH (reaction **9-12**), then cupric salts are oxidizing agents, and the OH group is found in a position ortho to that occupied by the alkyl group.[80] What is happening here is an initial oxidation to COOH, and then an example of reaction **3-20** (p. 511).

In a different kind of reaction, the methyl group of trinitrotoluene can be oxidized to an OH group in the *same* position, with $Na_2Cr_2O_7$, H_2SO_4, and

---

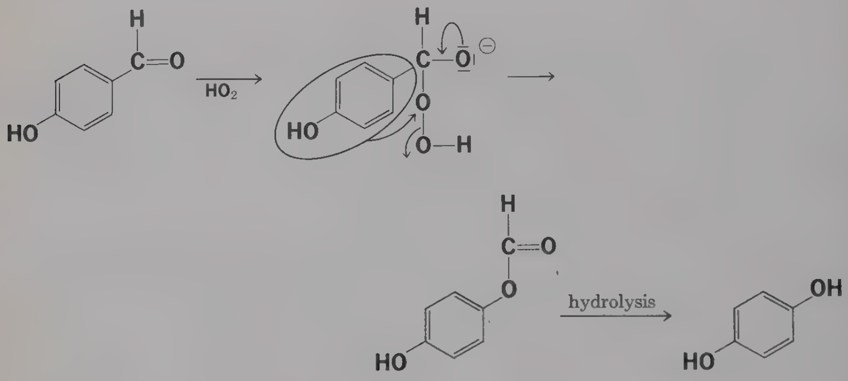
[78] Wiberg and Evans, *Tetrahedron* **8,** 313 (1960).

[79] Foster and Hickinbottom, *J. Chem. Soc.* **1960,** 680; Ferguson and Wims, *J. Org. Chem.* **25,** 668 (1960).

[80] Kaeding, *J. Org. Chem.* **26,** 3144 (1961).

HNO_3.[81] The sequence in this case seems to be (1) oxidation to COOH, (2) nucleophilic substitution of the COOH by NO_3^-, and (3) hydrolysis of the nitrate ester.

In a third kind of reaction, an aromatic aldehyde ArCHO is converted to a phenol ArOH upon treatment with alkaline H_2O_2, but there must be an OH or NH_2 group in the ortho or para position. This is called the *Dakin reaction*. The mechanism is probably similar to that of the Baeyer-Villiger reaction (**8-20**, p. 822):



OS **I**, 149; **III**, 759.

9-14 Oxidative decarboxylation

$$\mathrm{RCOOH} \xrightarrow{\mathrm{Pb(OAc)_4}} \mathrm{ROAc}$$

Lead tetraacetate cleaves carboxyl groups, replacing them with acetoxy groups, which may be hydrolyzed to OH groups.[82] However, there are usually many side products. The mechanism seems to be of the free-radical type.[83] First there is an interchange of ester groups:

$$\mathrm{Pb(OAc)_4} + \mathrm{RCOOH} \longrightarrow \mathrm{Pb(OAc)_3OCOR} \quad \text{or} \quad \underset{\mathbf{12}}{\mathrm{Pb(OAc)_2(OCOR)_2}}$$

Then the steps are (shown for **12**):

Initiation:

$$\underset{\mathbf{12}}{\mathrm{Pb(OAc)_2(OCOR)_2}} \longrightarrow \underset{\mathbf{13}}{\mathrm{Pb(OAc)_2(OCOR)}} + \mathrm{R\cdot} + \mathrm{CO_2}$$

---

[81] Dacons, Adolph, and Kamlet, *Tetrahedron* **19**, 791 (1963); Adolph, Dacons, and Kamlet, *Tetrahedron* **19**, 801 (1963).

[82] For example; see Büchi, Erickson, and Wakabayashi, *J. Am. Chem. Soc.* **83**, 927 (1961); Cope, Park, and Scheiner, *J. Am. Chem. Soc.* **84**, 4862 (1962).

[83] Kochi, *J. Am. Chem. Soc.* **87**, 1811, 3609 (1965); also see Starnes, *J. Am. Chem. Soc.* **86**, 5603 (1964); Davies and Waring, *Chem. Commun.* **1965**, 263.

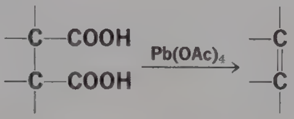
Propagation:

$$\mathrm{Pb(OAc)_2(OCOR)} \longrightarrow \mathrm{Pb(OAc)_2} + \mathrm{R\cdot} + \mathrm{CO_2}$$

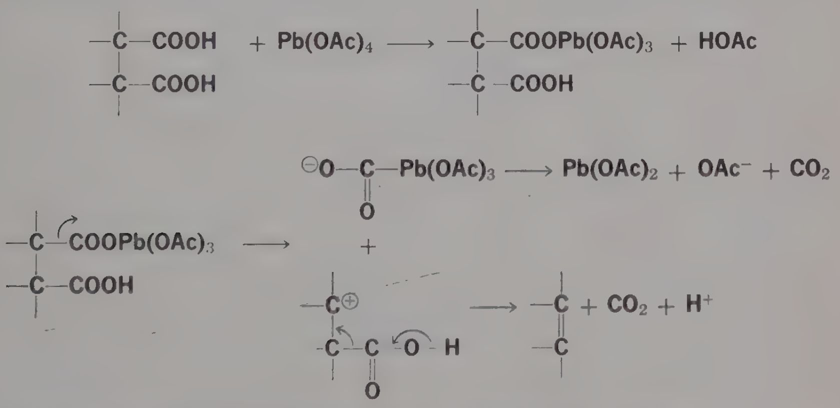
$$\mathrm{R\cdot} + \mathrm{Pb(OAc)_2(OCOR)_2} \longrightarrow \mathrm{Pb(OAc)(OCOR)_2} + \mathrm{ROAc}$$

The lead esters shown (**12** and **13**) represent one possibility only. It is also possible for other combinations of acyloxy groups to be present in both the 4 and the 3 oxidation state of lead. See also reaction **4-26** (p. 559).

9-15 Bisdecarboxylation

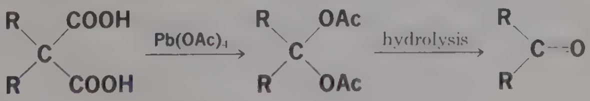


Compounds containing carboxyl groups on adjacent carbons (succinic acid derivatives) may be bisdecarboxylated with lead tetraacetate.[84] The elimination is stereoselective, but not stereospecific (both *meso*- and *dl*-2,3-diphenylsuccinic acid gave *trans*-stilbene),[85] and a concerted mechanism is thus unlikely (see Chapter 15). The following mechanism is not inconsistent with the data:



though a free-radical mechanism seems to hold in some cases.

Compounds containing geminal carboxyl groups (malonic acid derivatives) may also be bisdecarboxylated with lead tetraacetate, *gem*-diacetates (acylals) being produced, which are easily hydrolyzable to ketones:[85a]



The reaction is a special case of reaction **9-14.**

---

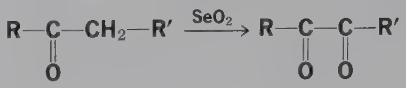
[84] Doering, Farber, and Sayigh, *J. Am. Chem. Soc.* **74**, 4370 (1952).

[85] Corey and Casanova, *J. Am. Chem. Soc.* **85**, 165 (1963).

[85a] Tufariello and Kissel, *Tetrahedron Letters* **1966**, 6145.

C. Reactions involving replacement of hydrogen by oxygen

9-16 Oxidation of methylene to carbonyl

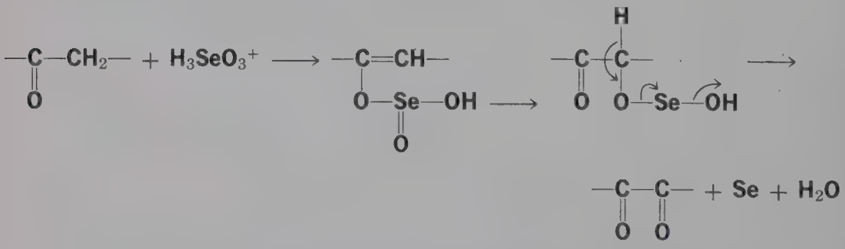


$$R-\underset{\underset{O}{\|}}{C}-CH_2-R' \xrightarrow{SeO_2} R-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-R'$$

Methylene groups α to a carbonyl can be oxidized with selenium dioxide to give α-dicarbonyl compounds.[86] Although SeO_2 is the reagent most often used, the reaction has also been carried out with N_2O_3 and other oxidizing agents. Other unsaturated groups—double and triple bonds and aromatic rings—also activate the methylene group. Substrates most easily oxidized contain two aryl groups on the CH_2, and these substrates can be oxidized with many oxidizing agents (see reaction **9-12**). With aryl alkanes the oxidation sometimes takes place on the β-carbon, e.g.,

$$PhCH_2CH_3 \longrightarrow PhCH_2CHO$$

It has been shown for the case where chromyl chloride is the oxidizing agent that there is initial α-oxidation followed by rearrangement.[87] Selenium dioxide may also be used to oxidize CH_3 groups to CHO (if activated by a carbonyl or other group), since it does not oxidize aldehydes further. The mechanism probably involves a selenate ester of the enol:[88]



OS **I,** 266; **II,** 509; **III,** 1, 420, 438; **IV,** 189, 229, 579. Also see OS **IV,** 23.

9-17 Oxidation of arylmethanes

$$ArCH_3 \xrightarrow{CrO_2Cl_2} ArCHO$$

Methyl groups on an aromatic ring may be oxidized to the aldehyde stage by several oxidizing agents. The reaction is a special case of reaction **9-16.** When the reagent is chromyl chloride (CrO_2Cl_2), the reaction is called the *Étard reaction,*[89] and the yields are high.[90] Another oxidizing agent is a mixture of CrO_3 and Ac_2O. In this case the reaction stops at the aldehyde stage because the initial product is $ArCH(OAc)_2$ (an acylal), which is resistant to further oxidation. Hydrolysis of the acylal gives the aldehyde. Oxidation of $ArCH_3$ to carboxylic acids is considered at reaction **9-12.**

---

[86] For a review, see Rabjohn, *Org. Reactions* **5**, 331–386 (1949).

[87] Wiberg, Marshall, and Foster, *Tetrahedron Letters* **1962**, 345.

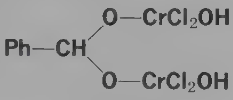
[88] Corey and Schaefer, *J. Am. Chem. Soc.* **82**, 918 (1960).

[89] The name Étard reaction is often applied to any oxidation with chromyl chloride, e.g., oxidation of glycols (reaction **9-8**), olefins (reaction **9-11**), etc.

[90] For a review, see Hartford and Darrin, *Chem. Rev.* **58**, 1–61 (1958), pp. 25–53.

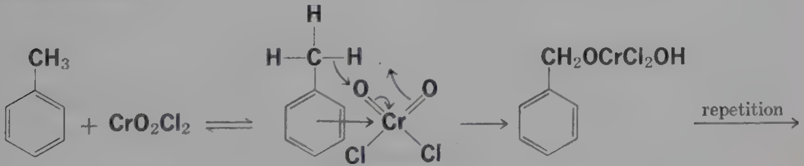
Conversion of $ArCH_3$ to ArCHO may also be achieved indirectly by bromination to give $ArCHBr_2$ (reaction **4-1**, p. 532), followed by hydrolysis (reaction **0-2**, p. 303).

The mechanism of the Étard reaction is not completely known. There is an insoluble complex formed upon addition of the reagents, which is hydrolyzed to the aldehyde. The complex is probably a kind of acylal, but what the structure is is not fully settled, though many proposals have been made as to its structure and as to how it is hydrolyzed.[90] It is known that $ArCH_2Cl$ is not an intermediate (see reaction **9-19**), since it reacts only very slowly with chromyl chloride. Magnetic susceptibility measurements[91] indicate that the complex from toluene is **14**, a structure first proposed by Étard. According to this proposal the reaction stops after only two hydrogens have been replaced because of the insolubility of **14**. There is disagreement on how **14** is formed, assuming that the complex has this structure. Both an ionic[92] and a free-radical[93] process have been proposed:



14

Ionic process:



π-Complex

Free-radical process:

$$ArCH_3 + Cl_2CrO_2 \longrightarrow ArCH_2\cdot + HO\dot{C}rOCl_2$$

$$ArCH_2\cdot + HO\dot{C}rOCl_2 \longrightarrow ArCH_2OCrCl_2OH \xrightarrow{\text{repetition}}$$

An entirely different structure for the complex was proposed by Nenitzescu and coworkers.[94] On the basis of electron-spin-resonance studies they proposed that the complex is $PhCH_2OCrCl_2OCrOCl_2OH$, which is isomeric with **14**. However, this view has been challenged by Wiberg and Eisenthal,[93] who interpret the esr result as being in accord with **14**.

OS **II,** 441; **III,** 641; **IV,** 31, 713.

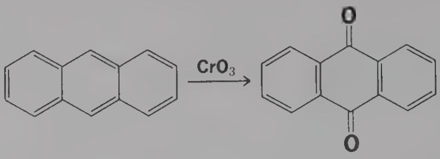
[91] Wheeler, *Can. J. Chem.* **38,** 2137 (1960).

[92] Stairs, *Can. J. Chem.* **42,** 550 (1964).

[93] Wiberg and Eisenthal, *Tetrahedron* **20,** 1151 (1964).

[94] Necsoiu, Balaban, Pascaru, Sliam, Elian, and Nenitzescu, *Tetrahedron* **19,** 1133 (1963).

9-18 Oxidation of aromatic hydrocarbons to quinones



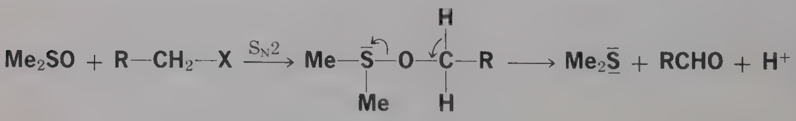
Condensed aromatic ring systems may be directly oxidized to quinones. Benzene cannot be so oxidized by strong oxidizing agents but can be electrolytically oxidized to benzoquinone.

OS **IV**, 698, 757. Also see OS **II**, 554.

9-19 Oxidation of primary halides and esters of primary alcohols to aldehydes

$$RCH_2Cl \xrightarrow{(CH_3)_2SO} RCHO$$

Primary alkyl halides (chlorides, bromides, and iodides) can be oxidized to aldehydes easily and in good yields with dimethyl sulfoxide.[95] Tosyl esters of primary alcohols may be similarly converted to aldehydes,[96] and epoxides give α-hydroxy aldehydes.[97] The reaction with tosyl esters represents an indirect way of oxidizing primary alcohols to aldehydes (reaction **9-3**). This type of oxidation may also be carried out without isolation of an intermediate ester: the alcohol is treated with dimethyl sulfoxide, dicyclohexylcarbodiimide, and anhydrous phosphoric acid.[98] In this way a primary alcohol may be converted to the aldehyde with no carboxylic acid being produced. A similar oxidation may be carried out with dimethyl sulfoxide and acetic anhydride.[99] Chloroformate esters (RCH_2OCOCl) may also be oxidized to aldehydes by treatment with dimethyl sulfoxide followed by Et_3N.[100] The mechanism of these dimethyl sulfoxide oxidations is probably as follows:[101]



$$Me_2SO + R{-}CH_2{-}X \xrightarrow{S_N2} Me{-}\underset{Me}{\overset{-}{S}}{-}O{-}\underset{H}{\overset{H}{C}}{-}R \longrightarrow Me_2\underline{\bar{S}} + RCHO + H^+$$

This mechanism predicts that secondary compounds should be oxidizable to ketones, and this is the case.

---

[95] Nace and Monagle, *J. Org. Chem.* **24**, 1792 (1959); Kornblum, Jones, and Anderson, *J. Am. Chem. Soc.* **81**, 4113 (1959); Johnson and Pelter, *J. Chem. Soc.* **1964**, 520; Traynelis and Hergenrother, *J. Am. Chem. Soc.* **86**, 298 (1964). For a review, see Epstein and Sweat, *Chem. Rev.* **67**, 247–260 (1967).

[96] Kornblum, Jones, and Anderson, Ref. 95.

[97] Cohen and Tsuji, *J. Org. Chem.* **26**, 1681 (1961).

[98] Pfitzner and Moffatt, *J. Am. Chem. Soc.* **87**, 5661, 5670 (1965); Fenselau and Moffatt, *J. Am. Chem. Soc.* **88**, 1762 (1966); Albright and Goldman, *J. Org. Chem.* **30**, 1107 (1965).

[99] Albright and Goldman, *J. Am. Chem. Soc.* **87**, 4214 (1965).

[100] Barton, Garner, and Wightman, *J. Chem. Soc.* **1964**, 1855.

[101] Hunsberger and Tien, *Chem. Ind.* (*London*) **1959**, 88.

Another way to oxidize primary alkyl halides to aldehydes is by the use of hexamethylenetetramine followed by water. However, this reaction, called the *Sommelet reaction,*[102] is limited to benzylic halides. The reaction is seldom useful when the R in RCH_2Cl is alkyl. The first part of the reaction is conversion to the amine $ArCH_2NH_2$ (reaction **0-45**, p. 332), which can be isolated. Reaction of the amine with excess hexamethylenetetramine gives the aldehyde. It is this last step which is the actual Sommelet reaction, though the entire process may be conducted without isolation of intermediates. Once the amine is formed, it is converted to an imine ($ArCH_2N{=}CH_2$) with formaldehyde liberated from the reagent. The key step then follows: transfer of hydrogen from another mole of the arylamine to the imine:

$$ArCH_2N{=}CH_2 + ArCH_2NH_2 \longrightarrow ArCH_2NHCH_3 + ArCH{=}NH$$

This last imine is then hydrolyzed by water to the aldehyde. Alternatively, the benzylamine may transfer hydrogen directly to hexamethylenetetramine, converting the latter to methylamine. The other product of the reaction is methylamine or $ArCH_2NHCH_3$, depending on whether hexamethylenetetramine is in excess or not. The actual mechanism of the hydrogen-transfer step is in doubt, but it probably begins with a hydride shift. Primary amines (including alkyl RCH_2NH_2) may also be oxidized to imines (and hence hydrolyzed to aldehydes or ketones) by benzophenone and ultraviolet light.[103]

Another way of converting a benzylic halide to an aldehyde is the *Kröhnke reaction,* which consists of treatment by pyridine, followed by *p*-nitrosodimethylaniline and then water.

OS **II,** 336; **III,** 811; **IV,** 690, 918, 932; **42,** 79; **46,** 81. Also see OS **45,** 55.

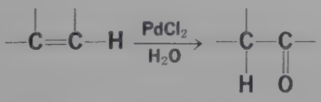
9-20 Oxidation of primary alcohols to carboxylic acids

$$RCH_2OH \xrightarrow{CrO_3} RCOOH$$

Primary alcohols can be oxidized to carboxylic acids by many strong oxidizing agents. The reaction may be looked upon as a combination of reactions **9-3** and **4-6** (p. 539). When acid conditions are used, a considerable amount of ester RCOOR is often isolated, though this is probably not formed by a combination of the acid with unreacted alcohol, but by a combination of intermediate aldehyde with unreacted alcohol to give an acetal or hemiacetal, which is oxidized to the ester.[104] Lactones may be prepared by oxidizing diols in which at least one OH is primary.

OS **I,** 138, 168; **IV,** 499, 677. Also see OS **III,** 745; **46,** 37.

9-21 Oxidation of olefins to aldehydes and ketones



$$-\overset{|}{C}{=}\overset{|}{C}-H \xrightarrow[H_2O]{PdCl_2} -\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{O}{\underset{\|}{C}}-$$

---

[102] For a review, see Angyal, *Org. Reactions* **8,** 197 (1954).

[103] Cohen and Baumgarten, *J. Am. Chem. Soc.* **87,** 2996 (1965).

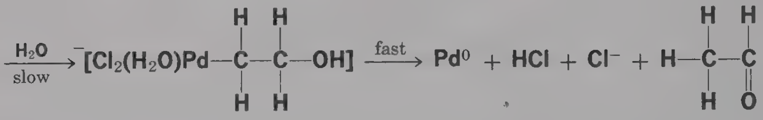
[104] Craig and Horning, *J. Org. Chem.* **25,** 2098 (1960).

Olefins may be oxidized to aldehydes and ketones by palladium chloride and similar salts of noble metals.[105] The reaction is used industrially to prepare acetaldehyde from ethylene, but it is also suitable for laboratory preparations.[106] The principal product is an aldehyde only from ethylene: with other olefins Markovnikov's rule is followed, and ketones are formed predominantly. There are two parts to the reaction: formation of a complex

$$C_2H_4 + PdCl_4^{=} \longrightarrow C_2H_4PdCl_3^- + Cl^-$$

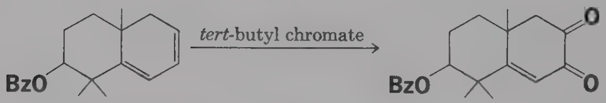
and hydrolysis of the complex, but the mechanism of each step is not certain. The following mechanism has been proposed for the second part:[107]

$$[C_2H_4PdCl_3]^- \underset{}{\overset{H_2O}{\underset{-Cl^-}{\rightleftharpoons}}} [C_2H_4PdCl_2(H_2O)] \overset{H_2O}{\underset{-H_3O^+}{\rightleftharpoons}} [C_2H_4PdCl_2(OH)]^-$$



$$\xrightarrow[\text{slow}]{H_2O} {}^{-}[Cl_2(H_2O)Pd-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-OH] \xrightarrow{\text{fast}} Pd^0 + HCl + Cl^- + H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{\overset{\|}{O}}{C}}$$

With some reagents it is possible to oxidize olefins to α-diketones, e.g.,[108]



9-22 Oxidation of primary amines to nitroso compounds

$$ArNH_2 \xrightarrow{H_2SO_5} Ar-N=O$$

Primary aromatic amines may be oxidized to nitroso compounds. Most often the conversion is accomplished by Caro's acid (H_2SO_5) or with H_2O_2,[109] but the reaction has also been performed with OF_2.[110] Hydroxylamines, which are probably intermediates in most cases, can sometimes be isolated, but under the reaction conditions they are generally oxidized to the nitroso compounds. Primary aliphatic amines may also be oxidized in this manner, but the nitroso compound is stable only if there is no α hydrogen. If there is an α hydrogen, the compound tautomerizes to the oxime.[111] The mechanism with H_2SO_5 has been postulated to be an example of category 5 (p. 856):[112]

---

[105] For reviews, see Smidt, Hafner, Jira, Sieber, Sedlmeier, and Sabel, *Angew. Chem. Intern. Ed. Engl.* **1**, 80–88 (1962); Smidt, *Chem. Ind.* (*London*) **1962**, 54–61.

[106] Clement and Selwitz, *J. Org. Chem.* **29**, 241 (1964), and references cited therein.

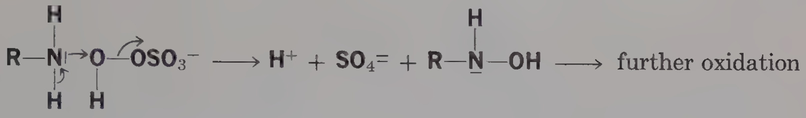
[107] Henry, *J. Am. Chem. Soc.* **88**, 1595 (1966). See also Jira, Sedlmeier, and Smidt, *Ann.* **693**, 99 (1966).

[108] Haynes, Redmore, and Timmons, *J. Chem. Soc.* **1963**, 2420.

[109] Holmes and Bayer, *J. Am. Chem. Soc.* **82**, 3454 (1960).

[110] Merritt and Ruff, *J. Am. Chem. Soc.* **86**, 1392 (1964).

[111] For example, see Kahr and Berther, *Chem. Ber.* **93**, 132 (1960).



OS **III,** 334.

9-23 Oxidation of primary amines, oximes, or nitroso compounds to nitro compounds

$$R_3CNH_2 \xrightarrow{KMnO_4} R_3CNO_2$$

$$R_2C{=}NOH \xrightarrow{F_3CCOOOH} R_2CHNO_2$$

Primary amines at a tertiary carbon can be oxidized in excellent yields to nitro compounds,[113] and this type of nitro compound is not easily prepared in other ways. The oxidizing agent is potassium permanganate. Primary amines at a secondary carbon and primary aromatic amines[114] may be oxidized to nitro compounds with peracetic acid. Oximes may be oxidized to nitro compounds with peroxytrifluoroacetic acid, among other ways.[113] Aromatic nitroso compounds are easily oxidized to nitro compounds by many oxidizing agents.

OS **III,** 334; **43,** 87.

9-24 Oxidation of mercaptans and other sulfur compounds to sulfonic acids

$$RSH \xrightarrow{HNO_3} RSO_3H$$

Mercaptans, sulfoxides, sulfones, disulfides, and other sulfur compounds may be oxidized to sulfonic acids with many oxidizing agents, though for synthetic purposes the reaction is most important for mercaptans.[114a] Among oxidizing agents used are boiling nitric acid and barium permanganate. Autoxidation (oxidation by atmospheric oxygen) may be accomplished in basic solution.[115] Mercaptans may also be oxidized to disulfides (reaction **9-31**). The oxidation of RCH_2SCOR (prepared by reaction **5-7,** p. 587) to RCH_2SO_3H with H_2O_2-HOAc affords a preparation of aliphatic sulfonic acids from olefins.[116]

OS **II,** 471; **III,** 226. Also see OS **40,** 99.

---

[112] Gragerov and Levit, *J. Gen. Chem. USSR* **30,** 3690 (1961).

[113] Kornblum, *Org. Reactions* **12,** 101–156 (1962), pp. 115–120.

[114] Emmons, *J. Am. Chem. Soc.* **79,** 5528 (1957).

[114a] For a review, see Gilbert, "Sulfonation and Related Reactions," pp. 217–239, Interscience Publishers, Inc., New York, 1965.

[115] Wallace and Schriesheim, *Tetrahedron* **21,** 2271 (1965).

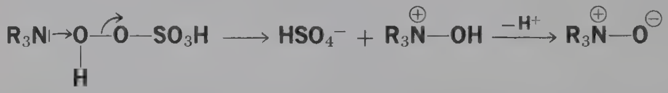
[116] Showell, Russell, and Swern, *J. Org. Chem.* **27,** 2853 (1962).

D. Reactions in which an unshared pair becomes bonded to oxygen

9-25 Oxidation of tertiary amines to amine oxides

$$R_3N \xrightarrow{H_2O_2} R_3\overset{\oplus}{N}-\overset{\ominus}{O}$$

Tertiary amines may be converted to amine oxides by oxidation. Hydrogen peroxide is often used, but peracids are also important reagents for this purpose. Pyridine and its derivatives are oxidized only by peracids.[117] In the attack by hydrogen peroxide there is first formed a trialkylammonium peroxide, a hydrogen-bonded complex represented as $R_3N{\cdot}H_2O_2$, which can be isolated.[118] The decomposition of this complex probably involves an attack by the OH^+ moiety of the H_2O_2. Oxidation with Caro's acid has been shown to proceed in this manner:[119]

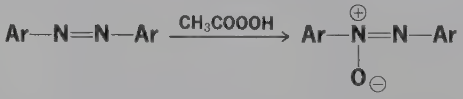


$$R_3N| \rightarrow \underset{H}{O}-O-SO_3H \longrightarrow HSO_4^- + R_3\overset{\oplus}{N}-OH \xrightarrow{-H^+} R_3\overset{\oplus}{N}-O^{\ominus}$$

This mechanism is the same as that of reaction **9-22**, and the products differ only because tertiary amine oxides cannot be further oxidized. The mechanism with other peracids is probably the same.

OS **IV**, 612, 704, 828.

9-26 Oxidation of azobenzenes to azoxybenzenes



$$Ar-N=N-Ar \xrightarrow{CH_3COOOH} Ar-\underset{O^{\ominus}}{\overset{\oplus}{N}}=N-Ar$$

Azo compounds may be oxidized to azoxy compounds by peracids.[120] The mechanism is probably the same as that of reaction **9-25.**

9-27 Oxidation of isonitriles to isocyanates

$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{C} \xrightarrow[Me_2SO]{Cl_2} R-N=C=O$$

Isonitriles have been oxidized to isocyanates with HgO and with O_3, as well as with a halogen and dimethyl sulfoxide. In the latter case the oxidizing agent is the halogen, which converts the isonitrile to $R-N=CCl_2$, which is hydrolyzed to the isocyanate.[121] Isonitriles may also be oxidized by nitrile oxides, which are thus reduced to nitriles:[122]

$$Ar-C\equiv\overset{\oplus}{N}-\underline{\bar{O}}|^{\ominus} + R-\overset{\oplus}{N}\equiv\overset{\ominus}{\bar{C}} \longrightarrow Ar-C\equiv N + R-N=C=O$$

Cyanide ion may be oxidized to cyanate ion with many oxidizing agents.

---

[117] Ioffe and Efros, *Russ. Chem. Rev.* **30,** 569–582 (1961), pp. 570–571.

[118] Oswald and Guertin, *J. Org. Chem.* **28,** 651 (1963).

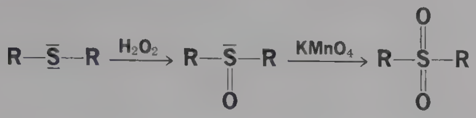
[119] Ogata and Tabushi, *Bull. Chem. Soc. Japan* **31,** 969 (1958).

[120] Swern, *Chem. Rev.* **45,** 1–68 (1949), p. 38.

[121] Johnson and Daughhetee, *J. Org. Chem.* **29,** 246 (1964).

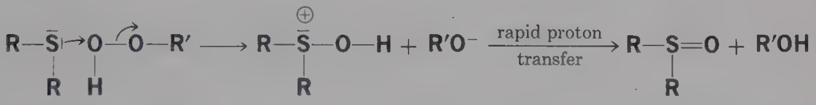
[122] Finzi and Arbasino, *Tetrahedron Letters* **1965,** 4645.

9-28 Oxidation of sulfides to sulfoxides and sulfones

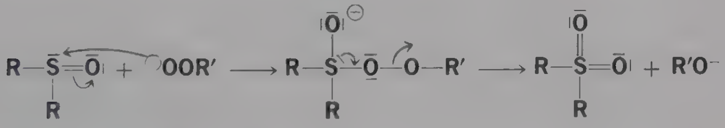


$$R{-}\bar{\underline{S}}{-}R \xrightarrow{H_2O_2} R{-}\overset{\displaystyle |}{\bar{S}}{-}R \xrightarrow{KMnO_4} R{-}\overset{O}{\overset{\|}{\underset{\underset{O}{\|}}{S}}}{-}R$$

Sulfides may be oxidized to sulfoxides by one mole of 30% H_2O_2 or by many other oxidizing agents. Sulfoxides may be further oxidized to sulfones by another mole of H_2O_2, $KMnO_4$, or a number of other agents. If enough oxidizing agent is present, sulfides may be directly converted to sulfones without isolation of the sulfoxides. These reactions give high yields, and many functional groups do not interfere. When the oxidizing agent is a peroxide, the mechanism of oxidation to the sulfoxide is similar to that of reaction **9-25**:[123]



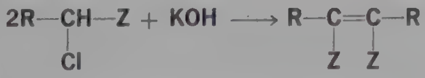
The second oxidation, which is slower than the first (which is why sulfoxides are so easily isolable), has the same mechanism in neutral or acid solution, but in basic solution it has been shown that the conjugate base of the peroxy compound ($R'OO^-$) also attacks the SO group as a nucleophile:[124]



OS **46,** 85. Also see OS **46,** 62.

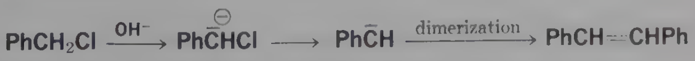
E. Oxidative coupling

9-29 Coupling involving carbanions



$$2R{-}\underset{\displaystyle Cl}{\underset{|}{CH}}{-}Z + KOH \longrightarrow R{-}\underset{\displaystyle Z}{\underset{|}{C}}{=}\underset{\displaystyle Z}{\underset{|}{C}}{-}R$$

Alkyl halides with an electron-withdrawing group on the halogen-bearing carbon may be dimerized to olefins by treatment with bases. Z may be nitro, aryl, etc. There are three possible mechanisms, two of them involving carbenes. In mechanism *a* there is simple dimerization of a carbene (the three mechanisms are illustrated for benzyl chloride):



$$PhCH_2Cl \xrightarrow{OH^-} Ph\overset{\ominus}{\bar{C}}HCl \longrightarrow Ph\bar{C}H \xrightarrow{\text{dimerization}} PhCH{=}CHPh$$

---

[123] Modena and Todesco, *J. Chem. Soc.* **1962,** 4920, and references cited therein.

[124] Curci and Modena, *Tetrahedron Letters* **1963,** 1749, *Tetrahedron* **22,** 1227 (1966); Curci, Giovine, and Modena, *Tetrahedron* **22,** 1235 (1966).

In mechanism *b* the carbanion does not go on to carbene but is a nucleophile, acting on a second molecule of halide as substrate:

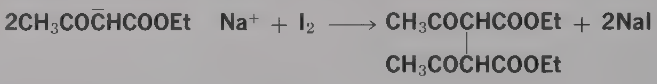
$$\mathrm{Ph\bar{C}HCl + PhCH_2Cl \xrightarrow[S_N]{} \underset{\textbf{15}}{PhCHClCH_2Ph} \xrightarrow{\text{elimination}} PhCH{=}CHPh}$$

The olefin is formed by elimination. In mechanism *c* there is a carbene, but it reacts with the carbanion instead of dimerizing:

$$\mathrm{Ph\bar{C}H + Ph\overset{\ominus}{C}HCl \longrightarrow Ph\overset{\ominus}{C}HCHClPh \xrightarrow{-Cl^-} PhCH{=}CHPh}$$

It has been shown, by isolation of **15**, that mechanism *b* operates in some cases,[125] while in other cases mechanism *c* has been demonstrated.[126]

A somewhat different type of coupling is observed when salts of β-keto esters and similar compounds are treated with iodine:



$$\mathrm{2CH_3CO\bar{C}HCOOEt\quad Na^+ + I_2 \longrightarrow \begin{array}{l} CH_3COCHCOOEt \\ \qquad\quad | \\ CH_3COCHCOOEt \end{array} + 2NaI}$$

The mechanism is probably as follows:

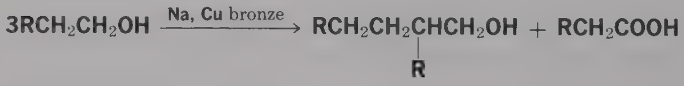
$$\mathrm{R^- + I_2 \longrightarrow RI + I^-}$$

$$\mathrm{RI + R^- \longrightarrow RR + I^-}$$

The second step is a Wurtz reaction (**0-81**, p. 353).

OS **II**, 273; **IV**, 372, 869. Also see OS **I**, 46.

9-30 The Guerbet reaction



$$\mathrm{3RCH_2CH_2OH \xrightarrow{Na,\ Cu\ bronze} RCH_2CH_2\underset{\underset{R}{|}}{C}HCH_2OH + RCH_2COOH}$$

Primary alcohols couple in the manner shown when treated with sodium and copper bronze. The reaction, called the *Guerbet reaction*, involves three molecules of alcohol, one of which is oxidized to the acid. Yields are about 30 to 50%.[127] The mechanism probably involves conversion of one mole of alcohol to the aldehyde, and then condensation of this with another mole of alcohol.[128]

9-31 Oxidation of mercaptans to disulfides

$$\mathrm{2RSH \xrightarrow{H_2O_2} RSSR}$$

Mercaptans are easily oxidized to disulfides. Hydrogen peroxide is the most common reagent, but many oxidizing agents give the reaction, though strong ones may give reaction **9-24.** Even the oxygen in the air oxidizes mercaptans on standing, if a small amount of base is present. The reaction is reversible (see reaction **9-55**), and the interconversion between cysteine and cystine is an important one in biochemistry. Thiol acids can likewise be coupled:

---

[125] Hauser, Brasen, Skell, Kantor, and Brodhag, *J. Am. Chem. Soc.* **78**, 1653 (1956).

[126] Swain and Thornton, *J. Am. Chem. Soc.* **83**, 4033 (1961).

[127] Weizmann, Bergmann, and Haskelberg, *Chem. Ind. (London)* **56**, 587 (1937); Weizmann, Bergmann, and Sulzbacker, *J. Org. Chem.* **15**, 54 (1950).

[128] Dvornikoff and Farrar, *J. Org. Chem.* **22**, 540 (1957).

$$2RCOS^- + I_2 \longrightarrow RCOSSCOR$$

The mechanism has been studied for several oxidizing agents and varies with the agent. For oxygen it is[129]

$$RSH + B^- \rightleftharpoons RS^- + BH$$
$$RS^- + O_2 \longrightarrow RS\cdot + \dot{O}_2{}^-$$
$$RS^- + \dot{O}_2{}^- \longrightarrow RS\cdot + O_2{}^{=}$$
$$2RS\cdot \longrightarrow RSSR$$
$$O_2{}^{=} + BH \longrightarrow OH^- + B^- + O_2$$

With respect to the sulfur, this mechanism is similar to that of reaction **4-14** (p. 549), involving as it does loss of a proton, reduction to a free radical, and radical coupling.

OS **III,** 86, 116.

9-32 Oxidation of amines to azo compounds

$$ArNH_2 \xrightarrow{MnO_2} Ar{-}N{=}N{-}Ar$$

Primary aromatic amines have been oxidized to azo compounds by a variety of oxidizing agents, among them MnO_2, lead tetraacetate, sodium perborate in acetic acid, and peracids.

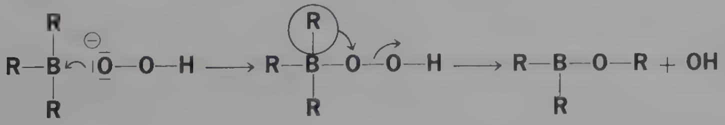
OS **40,** 18.

F. Oxidation to inorganic esters

9-33 Oxidation of trialkylboranes to borates

$$R_3B \xrightarrow[NaOH]{H_2O_2} (RO)_3B$$

Trialkylboranes may be oxidized to esters of boric acid by alkaline H_2O_2.[130] This reaction does not affect double or triple bonds, aldehydes, ketones, halides, or nitriles. The R group does not rearrange, and this reaction is a step in the hydroboration method of converting olefins to alcohols (reaction **5-13,** p. 599). The mechanism has been formulated, without much evidence, as involving a rearrangement from carbon to oxygen:[130]



---

[129] Wallace, Schriesheim, and Bartok, *J. Org. Chem.* **28,** 1311 (1963).

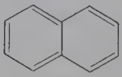
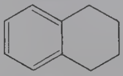
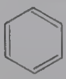
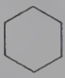
[130] For a review, see Brown, "Hydroboration," pp. 69–72, W. A. Benjamin, Inc., New York, 1962.

The other two R groups then similarly rearrange. Boranes may also be oxidized to borates with air, but the yields are lower. Free radicals seem to be involved here.[131]

Reductions: Selectivity. It is often necessary to reduce one group in a molecule without affecting another reducible group. It is usually possible to find a reducing agent which will do this. The most common broad-spectrum reducing agents are the metal hydrides and hydrogen (with a catalyst). Many different metal-hydride systems and hydrogenation catalysts have been investigated in order to find conditions under which a given group will be reduced without reducing another group in the same molecule. In Tables 6, 7, and 8 are listed the reactivity of various functional groups toward catalytic hydrogenation, $LiAlH_4$, and B_2H_6, respectively. Table 9 shows which groups can be reduced by catalytic hydrogenation and various metal hydrides. Of course, these tables cannot be exact, for the nature of R and the reaction conditions obviously affect reactivity. Nevertheless, the tables do give a fairly good indication of which reagents will reduce which groups.

The reactions in this section are grouped into classifications based on bond changes, similar to those used for the oxidation reactions. These sections are: reactions involving replacement of oxygen by hydrogen, reactions in

TABLE 6. The ease of reduction of various functional groups toward catalytic hydrogenation[132]
The groups are listed in approximate order of ease of reduction

Reaction	*Substrate*	*Product*	
0-78	RCOCl	RCHO	Easiest
9-42	RNO_2	RNH_2	
5-11	RC≡CR	RCH=CHR	
6-27	RCHO	RCH_2OH	
5-11	RCH=CHR	RCH_2CH_2R	
6-27	RCOR	RCHOHR	
0-75	$ArCH_2OR$	$ArCH_3$ + ROH	
6-29	RC≡N	RCH_2NH_2	
5-12			
9-39	RCOOR′	RCH_2OH + R′OH	
9-36	RCONHR′	RCH_2NHR	
5-12			Most difficult
9-35	$RCOO^-$	. . . .	Inert

---

[131] Mirviss, *J. Am. Chem. Soc.* **83**, 3051 (1961); Davies and Roberts, *Chem. Commun.* **1966**, 298.

[132] Taken from House, "Modern Synthetic Reactions," p. 9, W. A. Benjamin, Inc., New York, 1965.

TABLE 7. The ease of reduction of various functional groups with $LiAlH_4$ in ether[133] However, $LiAlH_4$ is a very powerful reagent, and much less selectivity is possible here than with most of the other metal hydrides

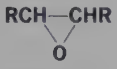
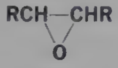
Reaction	*Substrate*	*Product*	
6-27	RCHO	RCH_2OH	Easiest
6-27	RCOR	RCHOHR	
9-41	RCOCl	RCH_2OH	
9-39	Lactone	Diol	
0-76		RCH_2CHOHR	
9-39	RCOOR′	$RCH_2OH + R'OH$	
9-35	RCOOH	RCH_2OH	
9-35	$RCOO^-$	RCH_2OH	
6-29	$RC{\equiv}N$	RCH_2NH_2	
9-42	RNO_2	RNH_2	
9-60	$ArNO_2$	$ArN{=}NAr$	Most difficult
5-11	$RCH{=}CHR$	. . . .	Inert

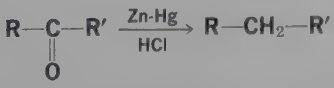
TABLE 8. The ease of reduction of various functional groups with diborane[134] It is evident that this reagent and $LiAlH_4$ (Table 7) complement each other

Reaction	*Substrate*	*Product*	
9-35	RCOOH	RCH_2OH	Easiest
5-13	$RCH{=}CHR$	$(RCH_2CHR)_3B$	
6-27	RCOR	RCHOHR	
0-76		RCH_2CHOHR	
9-39	RCOOR′	$RCH_2OH + R'OH$	Most difficult
0-78, 9-41	RCOCl	. . . .	Inert

which an oxygen is removed from the substrate, reduction with cleavage, and reductive coupling. Tables 4 and 5 (pp. 859–860) list reductions which were treated in previous chapters.

A. Reactions involving replacement of oxygen by hydrogen. In reactions **9-34** to **9-38**, a C=O is reduced to a CH_2 group.

9-34 Reduction of carbonyl to methylene in aldehydes and ketones



$$R{-}\underset{\underset{O}{\|}}{C}{-}R' \xrightarrow[HCl]{Zn\text{-}Hg} R{-}CH_2{-}R'$$

[133] Taken from Brown, "Hydroboration," p. 239, W. A. Benjamin, Inc., New York, 1962.

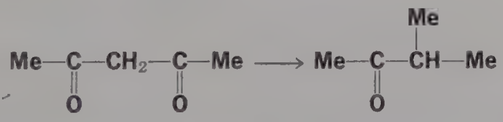
[134] Taken from Brown, Ref. 133, p. 250.

TABLE 9. Reactivity of various functional groups with some metal hydrides and toward catalytic hydrogenation[135]

	Reaction	$NaBH_4$ *in* EtOH	$NaBH_4$ + LiCl *in diglyme*	$NaBH_4$ + $AlCl_3$ *in diglyme*	$NaBH_4$ + BF_3 *in diglyme*	B_2H_6 *in THF*	*Bis-3-methyl-2-butylborane (disiamylborane) in THF*	LiAlH(O-*tert*-Bu)$_3$ *in THF*	LiAlH(OMe)$_3$ *in THF*	$LiAlH_4$ *in ether*	AlH_4 *in THF*	*Catalytic hydrogenation*
6-27	RCHO $\longrightarrow$ RCH_2OH	+	+	+	+	+	+	+	+	+	+	+
6-27	RCOR $\longrightarrow$ RCHOHR	+	+	+	+	+	+	+	+	+	+	+
0-78 9-41	RCOCl $\rightarrow$ RCHO $\rightarrow$ RCH_2OH	+	+	+	+[135a]	−	−	+	+	+	+	+
9-39	Lactone $\longrightarrow$ diol	+	+	+	+	+	+	. . .	+	+	+	+
9-39	RCOOR′ $\longrightarrow$ RCH_2OH + R′OH	−	+	+	±[135b]	±[135b]	−	−	+	+	+	+
9-35	RCOOH $\longrightarrow$ RCH_2OH	−	−	+	+	+	−	. . .	+	+	+	−
9-35	$RCOO^-$ $\longrightarrow$ RCH_2OH	−	−	−	−	−	. . .	. . .	. . .	+	. . .	−
6-29	RC≡N $\longrightarrow$ RCH_2NH_2	−	−	+	+	+	+	−	+	+	+	+
9-42 9-60	RNO_2 $\rightarrow$ RNH_2 $\rightarrow$ RN=NR	−	−	−	−	−	+	. . .	. . .	+	−	+
5-11	RCH=CHR $\longrightarrow$ RCH_2CH_2R	−	−	+	+	+	+	−	−	−	. . .	+

There are various ways of reducing the C=O group of aldehydes and ketones to CH_2. The two most important methods are the *Clemmensen reduction* and the *Wolff-Kishner reduction* (in the Russian literature this is called the *Kizhner reaction*). The Clemmensen reduction consists of heating the aldehyde or ketone with zinc amalgam and HCl.[136] Ketones are reduced more often than aldehydes. In the Wolff-Kishner reduction, the aldehyde or ketone is heated with hydrazine hydrate and a base.[137] When refluxing diethylene glycol is the solvent, the process is called the *Huang-Minlon modification* of the Wolff-Kishner reduction. The reaction can be carried out under more moderate conditions (room temperature) in dimethyl sulfoxide with potassium *tert*-butoxide as base.[138] The Clemmensen reduction is usually easier to perform, but it fails for acid-sensitive and high-molecular-weight substrates. For these cases the Wolff-Kishner reduction is quite useful.

Both methods are fairly specific for aldehydes and ketones and can be carried out with many other functional groups present. However, certain types of aldehyde and ketone do not give normal reduction products. Under Clemmensen conditions, α-hydroxy ketones give either ketones (hydrogenolysis of the OH, reaction **0-74**, p. 349) or olefins, and 1,3-diones usually undergo rearrangement exclusively, e.g.,[139]



$$\mathrm{Me{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}Me \longrightarrow Me{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{Me}{|}}{CH}{-}Me}$$

A similar rearrangement is observed upon Clemmensen reduction of unsaturated cyclic ketones.[140] Neither method is suitable for α,β-unsaturated ketones. These give pyrazolones under Wolff-Kishner conditions, while under Clemmensen conditions both groups of these molecules are normally reduced, and if only one group is reduced, it is the C=C bond. In the Clemmensen reduction, pinacols (reaction **9-57**) are often side products.

Other reagents have also been used to reduce the C=O of aldehydes and ketones to CH_2. Among these are catalytic hydrogenation at 180 to 250° and, for aryl ketones (ArCOR and ArCOAr), $LiAlH_4$-$AlCl_3$.[141] One carbonyl

[136] For a review, see Martin, *Org. Reactions* **1**, 155–209 (1942).

[137] For a review, see Todd, *Org. Reactions* **4**, 378–422 (1948).

[138] Cram, Sahyun, and Knox, *J. Am. Chem. Soc.* **84**, 1734 (1962); also see Grundon, Henbest, and Scott, *J. Chem. Soc.* **1963**, 1855.

[139] Cusack and Davis, *J. Org. Chem.* **30**, 2062 (1965); Wenkert and Kariv, *Chem. Commun.* **1965**, 570. However, Baker and Davis, *Chem. Ind. (London)* **1966**, 768, obtained about 24% normal reduction products in the case of 1-phenylbutan-1,3-dione.

[140] Davis and Woodgate, *J. Chem. Soc.* **1965**, 5943, *Chem. Commun.* **1966**, 65.

[141] Nystrom and Berger, *J. Am. Chem. Soc.* **80**, 2896 (1958).

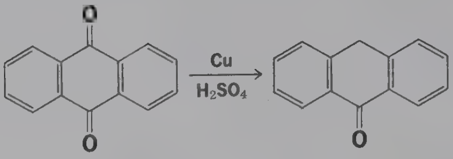
---

[135] Except for the column on catalytic hydrogenation, these data are from Brown, Ref. 133, p. 253, and Brown and Yoon, *J. Am. Chem. Soc.* **88**, 1464 (1966). Also see Brown, Weissman, and Yoon, *J. Am. Chem. Soc.* **88**, 1458 (1966); and Brown and Weissman, *J. Am. Chem. Soc.* **87**, 5614 (1965).

[135a] Fast reaction with $NaBH_4$ prior to addition of the BF_3.

[135b] Moderate reaction with longer reaction times.

group of 1,2-diketones may be selectively reduced by H_2S with an amine catalyst[142] or by HI in refluxing acetic acid.[143] One carbonyl group of quinones can be reduced with copper and sulfuric acid or with tin and HCl:[144]



An indirect method of accomplishing the reaction is reduction of tosylhydrazones ($R_2C{=}N{-}NHTs$) to R_2CH_2 with $LiAlH_4$ or $NaBH_4$.[145] Another indirect method is conversion of the aldehyde or ketone to a dithioacetal or ketal, and desulfurization of this (reaction **4-24,** p. 556).

The first step in the mechanism of the Wolff-Kishner reaction consists of formation of the hydrazone (reaction **6-21,** p. 674):

$$R_2C{=}O \longrightarrow R_2C{=}N{-}NH_2$$

It is this species which undergoes reduction in the presence of base, most probably in the following manner:

$$R_2C{=}N{-}NH_2 \overset{OH^-}{\rightleftharpoons} R_2CH{-}N{=}NH + OH^- \longrightarrow R_2\overset{\ominus}{\bar{C}}H + N_2 + H_2O$$

$$R_2\overset{\ominus}{\bar{C}}H + H_2O \longrightarrow R_2CH_2 + OH^-$$

Regarding the mechanism of the Clemmensen reduction, nothing much can be said. What has been reported in the literature is so contradictory[146] that no conclusions can be drawn, except that the corresponding alcohol is not an intermediate, since alcohols prepared in other ways fail to give the reaction. Note that the alcohol is not an intermediate in the Wolff-Kishner reduction either.

OS **I,** 60; **II,** 62, 499; **III,** 410, 444, 513, 786; **IV,** 203, 510; **43,** 34. Also see OS **IV,** 218.

9-35 Reduction of carboxylic acids to alcohols

$$RCOOH \xrightarrow{LiAlH_4} RCH_2OH$$

Carboxylic acids are easily reduced to primary alcohols by $LiAlH_4$.[147] The reaction does not stop at the aldehyde stage (but see reaction **0-79,** p. 352).

[142] Mayer, Hiller, Nitzschke, and Jentzsch, *Angew. Chem. Intern. Ed. Engl.* **2,** 370 (1963).

[143] Reusch and LeMahieu, *J. Am. Chem. Soc.* **86,** 3068 (1964).

[144] *Org. Syn.* **I,** 60, **II,** 62, respectively.

[145] Caglioti and Magi, *Tetrahedron* **19,** 1127 (1963); Caglioti and Grasselli, *Chem. Ind. (London)* **1964,** 153; Cagliotti, *Tetrahedron* **22,** 487 (1966); Fischer, Pelah, Williams, and Djerassi, *Chem. Ber.* **98,** 3236 (1965).

[146] See, for example, Poutsma and Wolthius, *J. Org. Chem.* **24,** 875 (1959); Nakabayashi, *J. Am. Chem. Soc.* **82,** 3900, 3906 (1960).

[147] For a review, see Gaylord, "Reduction with Complex Metal Hydrides," pp. 322–373, Interscience Publishers, Inc., New York, 1956.

The conditions are particularly mild, the reduction proceeding quite well at room temperature. Other hydrides have also been used, but not $NaBH_4$ (see Table 9). Catalytic hydrogenation is also ineffective. Diborane is particularly good for carboxyl groups (Table 8) and permits selective reduction of them in the presence of many other groups (though the reaction with double bonds takes place at about the same rate).[148]

OS **III**, 60.

9-36 Reduction of amides to amines

$$RCONH_2 \xrightarrow{LiAlH_4} RCH_2NH_2$$

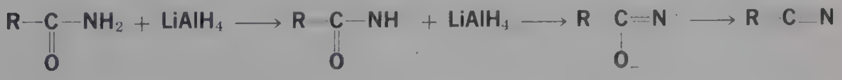
Amides can be reduced to amines with $LiAlH_4$[149] or by catalytic hydrogenation, though high temperatures are required for the latter. Even with $LiAlH_4$ the reaction is more difficult than the reduction of most other functional groups, and often other groups may be reduced without disturbing an amide function. $NaBH_4$ does not reduce amides. Substituted amides may be similarly reduced:

$$RCONHR' \longrightarrow RCH_2NHR'$$
$$RCONR'_2 \longrightarrow RCH_2NR'_2$$

Diborane is a good reducing agent for all three types of amide.[150] With some $RCONR'_2$, cleavage takes place, and the aldehyde (reaction **0-80**, p. 352) or alcohol is obtained. Thioamides may be reduced with hydrogen and Raney nickel.[151] Lactams are reduced to cyclic amines in high yields with $LiAlH_4$, though cleavage sometimes occurs here too. Imides are generally reduced on both sides, though it is sometimes possible to stop with just one. Both cyclic and acyclic imides have been reduced in this manner, though with acyclic imides, cleavage is often obtained, e.g.,[152]

$$PhN(COMe)_2 \longrightarrow PhNHEt$$

Nitriles have been isolated as intermediates in the treatment of unsubstituted amides with $LiAlH_4$.[153] The following mechanism has been proposed for the conversion of the amide to the nitrile:[153]



$$R{-}\underset{\underset{O}{\|}}{C}{-}NH_2 + LiAlH_4 \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}NH + LiAlH_4 \longrightarrow R{-}\underset{\underset{O_-}{|}}{C}{=}N \longrightarrow R{-}C{\equiv}N$$

OS **IV**, 339, 354, 564.

---

[148] Brown and Korytnyk, *J. Am. Chem. Soc.* **82**, 3866 (1960); Batrakov and Bergel'son, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1965**, 348.

[149] For a review of the reduction of amides, lactams, and imides with metallic hydrides, see Ref. 147, pp. 544–636.

[150] Brown and Heim, *J. Am. Chem. Soc.* **86**, 3566 (1964).

[151] Pettit and van Tamelen, *Org. Reactions* **12**, 356–529 (1962), pp. 385–389.

[152] Witkop and Patrick, *J. Am. Chem. Soc.* **74**, 3861 (1952).

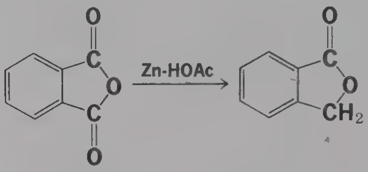
[153] Newman and Fukunaga, *J. Am. Chem. Soc.* **82**, 693 (1960).

9-37 Reduction of esters to ethers

$$\mathrm{RCOOR'} \xrightarrow[\mathrm{LiAlH_4}]{\mathrm{BF_3\text{-}etherate}} \mathrm{RCH_2OR'}$$

Esters and lactones have been reduced to ethers, though the more usual course is the obtention of two moles of alcohol (reaction **9-39**). Reduction to ethers has been accomplished with a reagent prepared from BF_3-etherate and either $LiAlH_4$, $LiBH_4$, or $NaBH_4$[154] and with catalytic hydrogenation. The reaction with the BF_3 reagent apparently succeeds with secondary R′, but not with primary R′, which give reaction **9-39.** Lactones give cyclic ethers.[155] Thiol esters RCOSR′ have been reduced to sulfides RCH_2SR'.[156]

9-38 Reduction of anhydrides to esters



Cyclic anhydrides can give lactones if reduced with Zn-HOAc, hydrogen and platinum, sodium ethoxide, or even $LiAlH_4$, although with the latter reagent diols are the more usual product (reaction **9-40**). Open-chain anhydrides usually give two moles of alcohol. $NaBH_4$ does not reduce anhydrides.

There are no *Organic Syntheses* references, but see OS **II**, 526, for a related reaction.

9-39 Reduction of esters to alcohols

$$\mathrm{RCOOR'} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{RCH_2OH} + \mathrm{R'OH}$$

$LiAlH_4$ reduces esters to give two moles of alcohol.[157] The reaction is of wide scope and has been used to reduce many esters. Where the interest is in obtaining R′OH, this represents a method of "hydrolyzing" esters. Lactones yield diols. $LiBH_4$ also gives the reaction, but $NaBH_4$ usually does not, though exceptions are known.[158] With $NaBH_4$ it is generally possible to reduce an aldehyde or ketone without reducing an ester function in the same molecule. However, $NaBH_4$ does reduce esters in the presence of certain compounds (see Table 9). Esters may also be reduced to alcohols by hydrogenation over copper chromite catalysts.[159] Before the discovery of

---

[154] Pettit, Ghatak, Green, Kasturi, and Piatak, *J. Org. Chem.* **26**, 1685 (1961); Pettit, Green, Kasturi, and Ghatak, *Tetrahedron* **18**, 953 (1962).

[155] See, for example, Pettit, Kasturi, Green, and Knight, *J. Org. Chem.* **26**, 4773 (1961); Edward and Ferland, *Chem. Ind.* (*London*) **1964**, 975.

[156] Eliel and Daignault, *J. Org. Chem.* **29**, 1630 (1964).

[157] For a review, see Ref. 147, pp. 391–531.

[158] For example, see Brown and Rapoport, *J. Org. Chem.* **28**, 3261 (1963).

[159] For a review, see Adkins, *Org. Reactions* **8**, 1–27 (1954).

$LiAlH_4$, the most common way of carrying out the reaction was with sodium in ethanol, a method known as the *Bouveault-Blanc procedure*. This procedure is still sometimes used where selectivity is necessary. See also reaction **9-37**.

OS **II**, 154, 325, 372, 468; **III**, 671; **IV**, 834.

9-40 Reduction of anhydrides to alcohols

$$\mathrm{RCOOCOR} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{2RCH_2OH}$$

$LiAlH_4$ usually reduces open-chain anhydrides to give two moles of alcohol. Cyclic anhydrides give either diols or lactones (see reaction **9-38**).

9-41 Reduction of acyl halides to alcohols

$$\mathrm{RCOCl} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{RCH_2OH}$$

Acyl halides are reduced to alcohols by $LiAlH_4$ or $NaBH_4$, as well as by other metal hydrides (Table 9), but not by diborane. The reaction may be regarded as a combination of reactions **9-34** and **0-73** (p. 348).

OS **IV**, 271.

9-42 Reduction of nitro compounds to amines

$$\mathrm{RNO_2} \xrightarrow[\mathrm{HCl}]{\mathrm{Zn}} \mathrm{RNH_2}$$

Both aliphatic and aromatic nitro compounds may be reduced to amines, though the reaction has been applied much more often to aromatic nitro compounds, owing to their greater availability. Many reducing agents have been used, among them Zn, Sn, or Fe (or sometimes other metals) and acid; catalytic hydrogenation; sulfides such as NaHS or $(NH_4)_2S$; AlH_3-$AlCl_3$; and hydrazine and a catalyst.[160] $LiAlH_4$ reduces aliphatic nitro compounds to amines, but with aromatic nitro compounds the products with this reagent are azo compounds (reaction **9-60**). Most metal hydrides, including $NaBH_4$, do not reduce nitro groups at all. Treatment of aromatic nitro compounds with $NaBH_4$ has resulted in reduction of the *ring* to a cyclohexane ring with the nitro group still intact[161] or in cleavage of the nitro group from the ring.[162] With $(NH_4)_2S$ it is possible to reduce just one of two nitro groups on an aromatic ring. The nitro groups of N-nitro compounds may also be reduced to amino groups; e.g., nitrourea, $NH_2CONHNO_2$, gives semicarbazide, $NH_2CONHNH_2$.

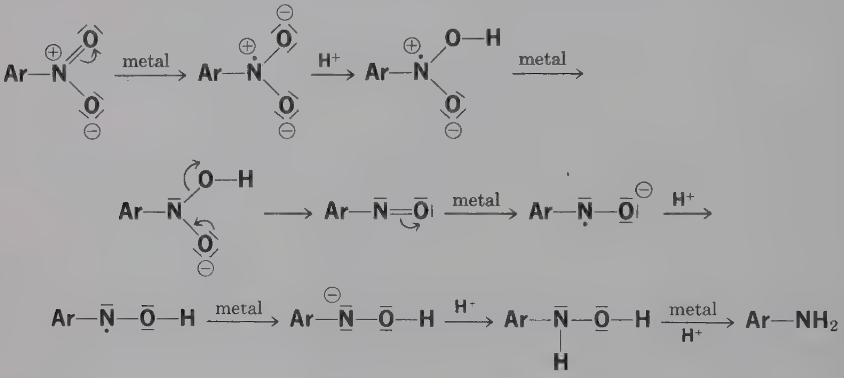
With some reducing agents, especially with aromatic nitro compounds, the reduction may be stopped at an intermediate stage, and hydroxylamines (reaction **9-43**), hydrazobenzenes (reaction **9-61**), azobenzenes (reaction **9-60**), and azoxybenzenes (reaction **9-59**) may be obtained in this manner. However, nitroso compounds, which are often postulated as intermediates, are too reactive to be isolated, if indeed they are intermediates. Reduction by metals in mineral acids cannot be stopped, but always produces the amine. The mechanisms of these reductions have been very little studied, though it is usually presumed that, at least with some reducing agents, nitroso compounds and hydroxylamines are intermediates. Both of these types of compounds give amines when exposed to most of these reducing agents (reaction **9-44**), and hydroxylamines can be isolated (reaction **9-43**). With metals and acid the following path has been suggested:[163]

---

[160] For a review of the use of hydrazine, see Furst, Berlo, and Hooton, *Chem. Rev.* **65**, 51–68 (1965), pp. 52–60. For a review of selective reductions of aliphatic nitro compounds without disturbance of other functional groups, see Ioffe, Tartakovskii, and Novikov, *Russ. Chem. Rev.* **35**, 19–32 (1966).

[161] Severin and Schmitz, *Chem. Ber.* **95**, 1417 (1962); Severin and Adams, *Chem. Ber.* **96**, 448 (1963).

[162] Kaplan, *J. Am. Chem. Soc.* **86**, 740 (1964).

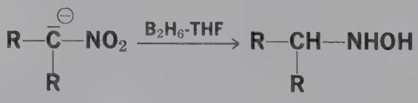


OS **I,** 52, 240, 455, 485; **II,** 130, 160, 175, 254, 447, 471, 501, 617; **III,** 56, 59, 63, 69, 73, 82, 86, 239, 242, 453; **IV,** 31, 357; **40,** 5, 96; **43,** 40; **44,** 34; **46,** 85.

9-43 Reduction of nitro compounds to hydroxylamines

$$ArNO_2 \xrightarrow[H_2O]{Zn} ArNHOH$$

When aromatic nitro compounds are reduced with zinc and water under neutral conditions, hydroxylamines are formed. Diborane in tetrahydrofuran reduces *aliphatic* nitro compounds (in the form of their salts) to hydroxylamines:[164]



$$R-\underset{\displaystyle R}{\overset{\ominus}{\underset{|}{\bar{C}}}}-NO_2 \xrightarrow{B_2H_6\text{-}THF} R-\underset{\displaystyle R}{\underset{|}{CH}}-NHOH$$

OS **I,** 445; **III,** 668; **IV,** 148.

9-44 Reduction of nitroso compounds and hydroxylamines to amines

$$RNO \xrightarrow[HCl]{Zn} RNH_2$$

$$RNHOH \xrightarrow[HCl]{Zn} RNH_2$$

---

[163] House, "Modern Synthetic Reactions," p. 74, W. A. Benjamin, Inc., New York, 1965.

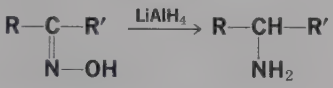
[164] Feuer, Bartlett, Vincent, and Anderson, *J. Org. Chem.* **31,** 2880 (1965).

Nitroso compounds and hydroxylamines may be reduced to amines by the same reagents which reduce nitro compounds (reaction **9-42**). N-Nitroso compounds are similarly reduced to hydrazines:

$$R_2N{-}NO \longrightarrow R_2N{-}NH_2$$

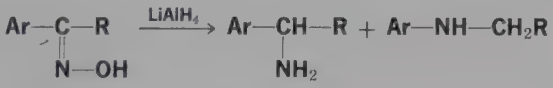
OS **I,** 511; **II,** 33, 202, 211, 418; **III,** 91; **IV,** 247.

9-45 Reduction of oximes to primary amines



$$R{-}\underset{\underset{\displaystyle N{-}OH}{\|}}{C}{-}R' \xrightarrow{LiAlH_4} R{-}\underset{\underset{\displaystyle NH_2}{|}}{CH}{-}R'$$

Both aldoximes and ketoximes may be reduced to primary amines with $LiAlH_4$. The reaction is slower than with ketones, so that, for example, PhCOCH=NOH gave 34% PhCHOHCH=NOH.[165] Other reducing agents which give this reduction are zinc and acetic acid, sodium ethoxide, and sodium and methanol in liquid ammonia.[166] Catalytic hydrogenation is also effective. With some oximes (usually aromatic), secondary amines arising from a rearrangement are side products and sometimes the main products:[167]



$$Ar{-}\underset{\underset{\displaystyle N{-}OH}{\|}}{C}{-}R \xrightarrow{LiAlH_4} Ar{-}\underset{\underset{\displaystyle NH_2}{|}}{CH}{-}R + Ar{-}NH{-}CH_2R$$

With other oximes, aziridines may be produced.[168]

Oximes may also be reduced to hydroxylamines (reaction **6-28,** p. 682).

OS **II,** 318; **III,** 513; **40,** 21, 24.

9-46 Reduction of miscellaneous nitrogen compounds

$$R{-}N{=}C{=}O \xrightarrow{LiAlH_4} R{-}NH{-}CH_3$$

$$R{-}N{=}C{=}S \xrightarrow{LiAlH_4} R{-}NH{-}CH_3$$

$$Ar{-}N{=}N{-}Ar \xrightarrow[\text{catalyst}]{H_2} Ar{-}NH{-}NH{-}Ar$$

$$R{-}N_3 \xrightarrow{LiAlH_4} RNH_2$$

$$ArN_2^+ \quad Cl^- \xrightarrow{Na_2SO_3} ArNHNH_2$$

---

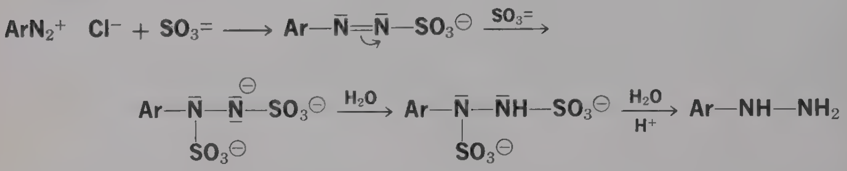
[165] Felkin, *Compt. rend.* **230,** 304 (1950).

[166] Terent'ev and Gusar', *J. Gen. Chem. USSR* **35,** 124, 128 (1965).

[167] Rerick, Trottier, Daignault, and DeFoe, *Tetrahedron Letters* **1963,** 629; Petrarca and Emery, *Tetrahedron Letters* **1963,** 635.

[168] Kitahonoki, Kotera, Matsukawa, Miyazaki, Okada, Takahashi, and Takano, *Tetrahedron Letters* **1965,** 1059.

Isocyanates and isothiocyanates are reduced to methylamines, and azides to primary amines, upon treatment with $LiAlH_4$. $LiAlH_4$ does not usually reduce azo compounds (indeed these are the products from $LiAlH_4$ reduction of nitro compounds, reaction **9-60**), but these may be reduced to hydrazo compounds by catalytic hydrogenation. Diazonium salts are reduced to hydrazines by sodium sulfite. This reaction probably has a nucleophilic mechanism:[169]

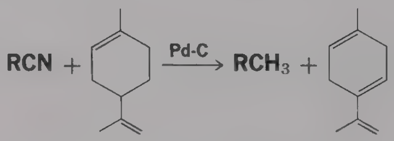


$$ArN_2^+ \ \ Cl^- + SO_3^= \longrightarrow Ar-\bar{N}=\bar{N}-SO_3^\ominus \xrightarrow{SO_3^=}$$

$$Ar-\underset{\displaystyle SO_3^\ominus}{\underset{|}{\bar{N}}}-\overset{\ominus}{\bar{N}}-SO_3^\ominus \xrightarrow{H_2O} Ar-\underset{\displaystyle SO_3^\ominus}{\underset{|}{\bar{N}}}-\bar{N}H-SO_3^\ominus \xrightarrow[H^+]{H_2O} Ar-NH-NH_2$$

The initial product is a salt of a hydrazinesulfonic acid, which is converted to the hydrazine by acid treatment.

A cyano group can be reduced to a methyl group by treatment with a terpene such as limonene (**16**) (which acts as reducing agent) in the presence of palladium-charcoal:[170]



16

R may be alkyl or aryl.

OS **I**, 442; **III**, 475; **45**, 47. Also see OS **43**, 1.

9-47 Reduction of sulfonyl halides to mercaptans

$$RSO_2Cl \xrightarrow{LiAlH_4} RSH$$

Mercaptans may be prepared by the reduction of sulfonyl halides with $LiAlH_4$. Usually, the reaction is carried out on aromatic sulfonyl chlorides. Zinc and acetic acid, and HI also give the reduction. Disulfides, RSSR, may also be produced. For the reduction of sulfonyl chlorides to sulfinic acids, see reaction **0-103** (p. 374).

OS **I**, 504; **IV**, 695; **40**, 80.

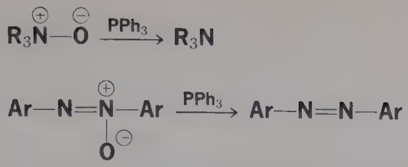
B. Reactions in which an oxygen is removed from the substrate

9-48 Reduction of amine oxides and azoxy compounds

---

[169] Huisgen and Lux, *Chem. Ber.* **93**, 540 (1960).

[170] Kindler and Lührs, *Chem. Ber.* **99**, 227 (1966).



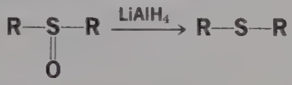
$$R_3\overset{\oplus}{N}-\overset{\ominus}{O} \xrightarrow{PPh_3} R_3N$$

$$Ar-N=\underset{\underset{\ominus}{O}}{\overset{\oplus}{N}}-Ar \xrightarrow{PPh_3} Ar-N=N-Ar$$

Amine oxides and azoxy compounds (both alkyl and aryl) may be reduced practically quantitatively with triphenylphosphine. Other reducing agents, e.g., $LiAlH_4$, PCl_3, and sulfur, have also been used. Nitrile oxides $R-C\equiv\overset{\oplus}{N}-\overset{\ominus}{O}$ may be reduced to nitriles with trialkylphosphines.[171]

OS **IV**, 166.

9-49 Reduction of sulfoxides and sulfones



$$R-\underset{\underset{O}{\|}}{S}-R \xrightarrow{LiAlH_4} R-S-R$$

Sulfoxides may be reduced to sulfides, by $LiAlH_4$ and other reagents, among them triphenylphosphine.[172] Sulfones, however, are usually stable to reducing agents, though they have been reduced to sulfides with $LiAlH_4$.[173] Both sulfoxides and sulfones may be reduced by heating with sulfur (which is oxidized to SO_2), though the reaction with sulfoxides proceeds at a lower temperature. It has been shown by using substrate labeled with ^{35}S that sulfoxides simply give up the oxygen to the sulfur, but that the reaction with sulfones is more complex, since about 75% of the original radioactivity of the sulfone is lost.[174] This indicates that most of the sulfur in the sulfide product comes in this case from the *reagent*.

9-50 Reduction of hydroperoxides

$$R-O-O-H \xrightarrow{LiAlH_4} ROH$$

Hydroperoxides may be reduced to alcohols with $LiAlH_4$ or by catalytic hydrogenation. This functional group is very susceptible to catalytic hydrogenation, as shown by the fact that a double bond may be present in the same molecule without being reduced.[175]

9-51 Reduction of nitro compounds to oximes

$$RCH_2NO_2 \xrightarrow{SnCl_2} RCH=NOH$$

Nitro compounds which contain an α hydrogen may be reduced to oximes with stannous chloride.

OS **IV**, 932.

[171] Grundmann and Frommeld, *J. Org. Chem.* **30**, 2077 (1965).

[172] Ray, Shaw, and Smith, *Nature* **196**, 372 (1962); Szmant and Cox, *J. Org. Chem.* **31**, 1595 (1966).

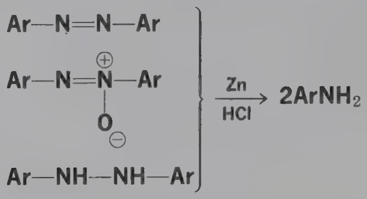
[173] Bordwell and McKellin, *J. Am. Chem. Soc.* **73**, 2251 (1951).

[174] Oae and Kawamura, *Bull. Chem. Soc. Japan* **36**, 163 (1963).

[175] Rebeller and Clément, *Bull. Soc. chim. France* **1964**, 1302.

C. Reduction with cleavage

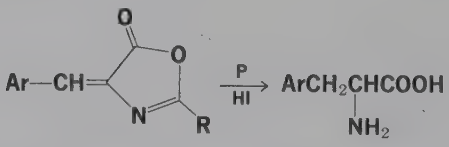
9-52 Reduction of azo, azoxy, and hydrazo compounds to amines



Azo, azoxy, and hydrazo compounds may all be reduced to amines. Metals (notably zinc) and acids, and $Na_2S_2O_4$ are frequently used as reducing agents. Diborane reduces azo compounds to amines, though it does not reduce nitro compounds.[176] $LiAlH_4$ does not reduce hydrazo compounds or azo compounds, though with the latter, hydrazo compounds are sometimes isolated. With azoxy compounds, $LiAlH_4$ gives only azo compounds (reaction **9-48**).

OS **I**, 49; **II**, 35, 39; **III**, 360. Also see OS **II**, 290.

9-53 Reduction of azlactones



The reduction of azlactones (with phosphorus and hydrogen iodide) provides a means of converting glycine into aromatic amino acids, since the azlactones may be prepared by the condensation of aromatic aldehydes with an N-acylglycine (reaction **6-42**, p. 698).

OS **II**, 489.

9-54 Reduction of peroxides

$$R{-}O{-}O{-}R \xrightarrow{LiAlH_4} 2ROH$$

Peroxides are cleaved to two moles of alcohol by $LiAlH_4$. Peroxides may be reduced to ethers with $P(OEt)_3$:[177]

$$ROOR + P(OEt)_3 \longrightarrow ROR + OP(OEt)_3$$

Disulfides may be similarly converted to sulfides.[178] Acyl peroxides are converted to anhydrides.

---

[176] Brown and Subba Rao, *J. Am. Chem. Soc.* **82**, 681 (1960).

[177] Horner and Jurgeleit, *Ann.* **591**, 138 (1955).

[178] Jacobson, Harvey, and Jensen, *J. Am. Chem. Soc.* **77**, 6064 (1955).

9-55 Reduction of disulfides to mercaptans

$$\text{RSSR} \xrightarrow[\text{H}^+]{\text{Zn}} 2\text{RSH}$$

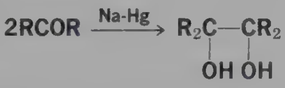
Disulfides may be reduced to mercaptans by mild reducing agents such as zinc and dilute acid. Often the reduction may be accomplished simply by heating with alkali, since OH^- gives RSOH and RS^- by a nucleophilic attack on the sulfur, and RSOH readily loses oxygen to give another mole of RS^-. $LiAlH_4$ has also been used.

OS **II**, 580. Also see OS **IV**, 295.

9-56 Reduction of ozonides. See reaction **9-10**.

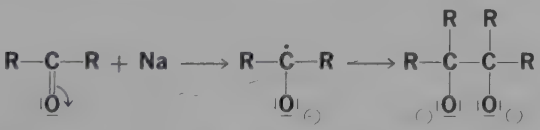
D. Reductive coupling

9-57 Bimolecular reduction of aldehydes and ketones

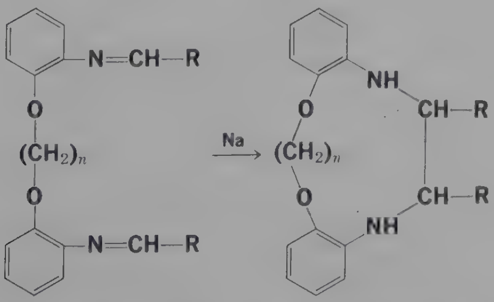


$$2\text{RCOR} \xrightarrow{\text{Na-Hg}} \underset{\text{OH}}{\underset{|}{\text{R}_2\text{C}}}-\underset{\text{OH}}{\underset{|}{\text{CR}_2}}$$

Pinacols may be synthesized by reduction of aldehydes and ketones with active metals such as sodium, magnesium, or aluminum. Aromatic ketones give better yields than aliphatic ones. Other reducing agents have been used, including electrochemical and photochemical methods. The use of a Mg-MgI_2 mixture has been called the *Gomberg-Bachmann pinacol synthesis*. As with a number of other reactions involving sodium, there is a direct electron transfer here, converting the ketone or aldehyde to a ketyl, which couples:

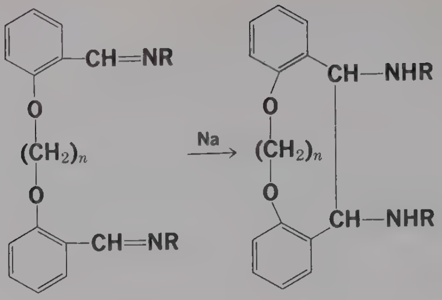


A closely related reaction is bimolecular coupling of imines with sodium. This reaction has been used to close large rings in two ways:[179]



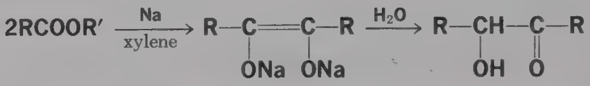
---

[179] Jaunin and Holl, *Helv. Chim. Acta* **41**, 1783 (1958); Jaunin and Magnetat, *Helv. Chim. Acta* **42**, 328 (1959); Bastian and Jaunin, *Helv. Chim. Acta* **46**, 1248 (1963).



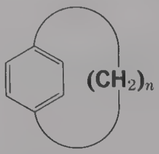
OS **I**, 459; **II**, 71.

9-58 The acyloin condensation



$$2RCOOR' \xrightarrow[\text{xylene}]{Na} R-\underset{ONa}{\underset{|}{C}}=\underset{ONa}{\underset{|}{C}}-R \xrightarrow{H_2O} R-\underset{OH}{\underset{|}{CH}}-\underset{O}{\underset{\|}{C}}-R$$

When esters are heated with sodium in refluxing ether or benzene, a bimolecular reduction takes place, and the product is an α-hydroxy ketone (called an acyloin).[180] The reaction, called the *acyloin condensation,* is quite successful when R is alkyl. Acyloins with long chains have been prepared in this way, for example, $R = C_{17}H_{35}$, but for high-molecular-weight esters, toluene or xylene is used as the solvent. The acyloin condensation has been used with great success, in boiling xylene, to prepare cyclic acyloins from diesters.[181] The yields are 50 to 60% for the preparation of six- and seven-membered rings, 30 to 40% for eight- and nine-membered, and 60 to 95% for rings of ten to twenty members. Even larger rings have been closed in this manner. This is the best way of closing rings of ten members or more. The reaction has been used to close four-membered rings,[182] though this is generally not successful. Small traces of oxygen greatly reduce the yields; hence the reaction must be conducted in an extremely pure nitrogen atmosphere. The presence of double or triple bonds does not interfere.[183] Even a benzene ring may be present, and many paracyclophane derivatives (**17**) with $n = 9$ or more have been synthesized in this manner.[184]



17

---

[180] For a review, see McElvain, *Org. Reactions* **4**, 256–268 (1948).

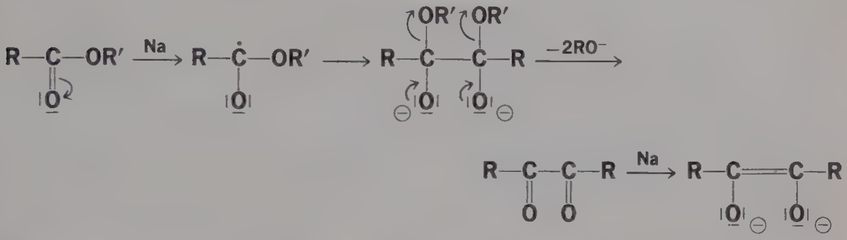
[181] For a review of cyclizations by means of the acyloin condensation, see Finley, *Chem. Rev.* **64**, 573–589 (1964).

[182] Cope and Herrick, *J. Am. Chem. Soc.* **72**, 983 (1950); Bloomfield and Irelan, *J. Org. Chem.* **31**, 2017 (1966).

[183] Cram and Gaston, *J. Am. Chem. Soc.* **82**, 6386 (1960).

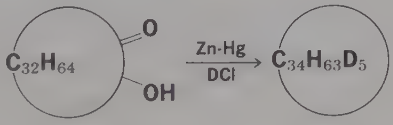
[184] For a review, see Cram, *Record Chem. Progr.* (*Kresge-Hooker Sci. Lib.*) **20**, 71 (1959).

The mechanism is not known with certainty, but it is presumed that the diketone RCOCOR is an intermediate, since small amounts of it are usually isolated as side products, and when it is resistant to reduction (for example, *tert*-Bu—CO—CO—*tert*-Bu), it is the major product. A possible sequence (analogous to that of reaction **9-57**) is



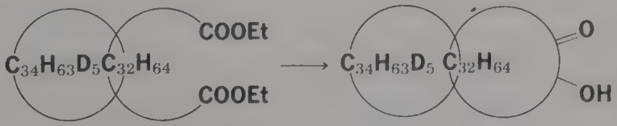
In order to account for the ready formation of large rings, which means that the two ends of the chain must approach each other even though this is conformationally unfavorable for long chains, it may be postulated that the two ends become attached to nearby sites on the surface of the sodium.

The acyloin condensation was used in an ingenious manner to prepare the first reported *catenane*, a compound with rings which are held together not by any valence forces, but as links of a chain are held together. The catenane (**18**)[185] was prepared in the following manner: an acyloin condensation was performed on the diethyl ester of the C_{34} dicarboxylic acid (tetratriacontandioic acid) to give the cyclic acyloin **19**. This was reduced by a Clemmensen reduction with DCl in D_2O instead of HCl in H_2O, thus producing a C_{34} cycloalkane containing deuterium (**20**):[186]



19 20

20 contained about 5 atoms of deuterium per molecule. The reaction was then repeated, this time *in a* 1:1 *mixture of xylene and* **20** *as solvent.* It was hoped that some of the molecules of ester would be threaded through **20** before they closed:



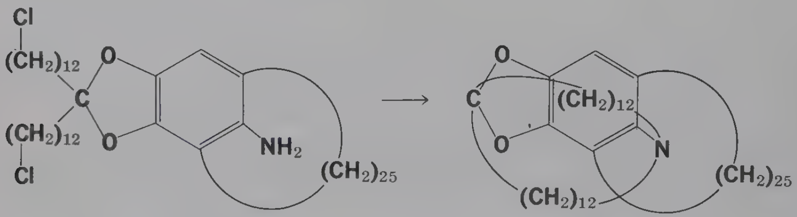
18

---

[185] Strictly speaking, the name caten*ane* should be restricted to alkanes, the more general name being catena compounds.

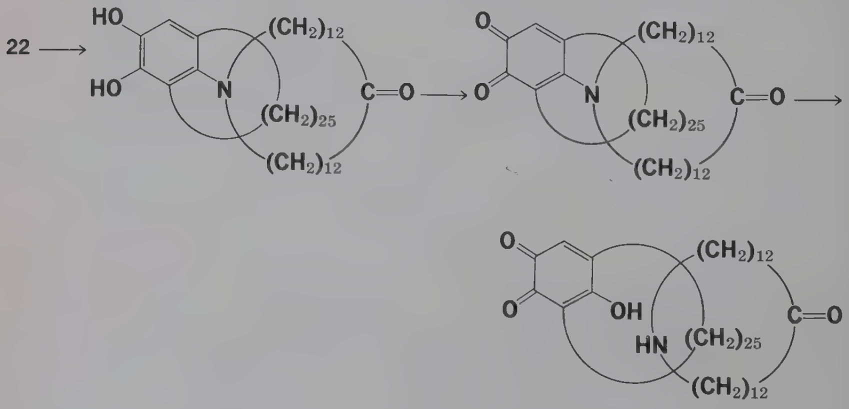
[186] This work was done by Wasserman, *J. Am. Chem. Soc.* **82**, 4433 (1960).

The first thing that was done with the product was to remove, by chromatography, the **20** which had been used as the solvent. The remaining material still contained deuterium, as determined by infrared spectra, even with all the **20** gone. This was strong evidence that the material consisted not only of **19**, but also of **18**. As further evidence, the mixture was oxidized to open up the acyloin rings (reaction **9-8**). From the oxidation product was isolated the C_{34} diacid (as expected), *containing no deuterium,* and **20**, containing deuterium. The total yield of **18** and **19** was 5 to 20%, but the percentage of **18** in this mixture was only about 1 to 2%.[186] This synthesis of a catenane produced only a small yield and relied on chance, on the probability that a diester molecule would be threaded through **20** before it closed. More recently, a *directed* synthesis of a catena compound has been reported.[187] The key step in this synthesis was formation of a tertiary amine by reaction **0-44** (p. 331):



21 **22**

Sterically, one of the halide groups of **21** is above the plane, and the other below it, so that ring closure must occur *through* the 28-membered ring. After **22** was formed, the acetal was cleaved (reaction **6-6**, p. 661). It was now necessary to cleave the remaining bond holding the two rings together, the C—N bond. This was done by oxidation to the *ortho*-quinone (reaction **9-4**), which converted the amine function to an enamine, which was hydrolyzable (reaction **6-15**, p. 667) with acid, to give the catena compound (**23**):



23

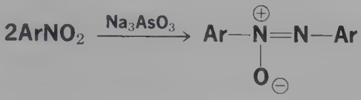
---

[187] Schill and Lüttringhaus, *Angew. Chem. Intern. Ed. Engl.* **3**, 546 (1964); Schill, *Chem. Ber.* **98**, 2906 (1965), **99**, 2689 (1966), **100**, 2021 (1967), *Ann.* **695**, 65 (1966).

The original large ring (of **21**) was closed by a Thorpe-Ziegler reaction (**6-46**, p. 709) after an attempted acyloin condensation proved unsuccessful.

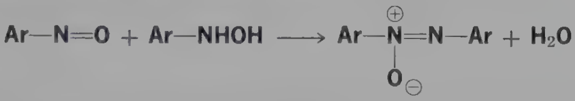
OS **II**, 114; **IV**, 840.

9-59 Reduction of nitro to azoxy compounds



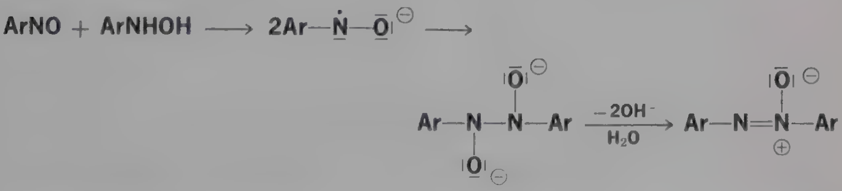
$$2\mathrm{ArNO_2} \xrightarrow{\mathrm{Na_3AsO_3}} \mathrm{Ar}-\underset{\substack{|\\ \mathrm{O}^{\ominus}}}{\overset{\oplus}{\mathrm{N}}}=\mathrm{N}-\mathrm{Ar}$$

Azoxy compounds may be obtained from nitro compounds with certain reducing agents, notably sodium arsenite, sodium ethoxide, and glucose. KBF_4 produces azoxy compounds only when there are electron-withdrawing groups on the ring.[188] The most probable mechanism is that one molecule of nitro compound is reduced to a nitroso compound and another to a hydroxylamine (reaction **9-43**), and these combine:



$$\mathrm{Ar}-\mathrm{N}=\mathrm{O} + \mathrm{Ar}-\mathrm{NHOH} \longrightarrow \mathrm{Ar}-\underset{\substack{|\\ \mathrm{O}^{\ominus}}}{\overset{\oplus}{\mathrm{N}}}=\mathrm{N}-\mathrm{Ar} + \mathrm{H_2O}$$

Nitroso compounds and hydroxylamines do combine to give azoxy compounds. The combination step is rapid compared to the reduction process.[189] The mechanism of the combination step involves conversion of both intermediates into radicals or anion-radicals, which have been detected by electron-spin resonance.[190] In the presence of base, nitrosobenzene anion-radicals are formed, which couple:



$$\mathrm{ArNO} + \mathrm{ArNHOH} \longrightarrow 2\mathrm{Ar}-\dot{\underline{\mathrm{N}}}-|\underline{\overline{\mathrm{O}}}|^{\ominus} \longrightarrow \mathrm{Ar}-\underset{\substack{|\\ |\underline{\mathrm{O}}|^{\ominus}}}{\mathrm{N}}-\overset{\substack{|\overline{\mathrm{O}}|^{\ominus}\\ |}}{\mathrm{N}}-\mathrm{Ar} \xrightarrow[\mathrm{H_2O}]{-2\mathrm{OH}^-} \mathrm{Ar}-\mathrm{N}=\underset{\oplus}{\overset{\substack{|\overline{\mathrm{O}}|^{\ominus}\\ |}}{\mathrm{N}}}-\mathrm{Ar}$$

This mechanism is consistent with the following result: when nitrosobenzene and phenylhydroxylamine are coupled, ^{18}O and ^{15}N labeling show that the two nitrogens and the two oxygens become equivalent.[191] Nitroso compounds may be reduced to azoxy compounds with triphenyl- or triethylphosphine.[192]

OS **II**, 57.

9-60 Reduction of nitro to azo compounds

$$2\mathrm{ArNO_2} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{Ar}-\mathrm{N}=\mathrm{N}-\mathrm{Ar}$$

---

[188] Shine and Mallory, *J. Org. Chem.* **27**, 2390 (1962).

[189] Ogata and Mibae, *J. Org. Chem.* **27**, 2048 (1962).

[190] Russell and Geels, *J. Am. Chem. Soc.* **87**, 122 (1965).

[191] Shemyakin, Maimind, and Vaichunaite, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1957**, 1260; Oae, Fukumoto, and Yamagami, *Bull. Chem. Soc. Japan* **36**, 728 (1963).

[192] Bunyan and Cadogan, *J. Chem. Soc.* **1963**, 42.

Nitro compounds may be reduced to azo compounds with various reducing agents, of which $LiAlH_4$ and zinc and alkali are the most common. With many of these reagents, slight differences in conditions may lead either to the azo or azoxy (reaction **9-59**) compound. Analogously to reaction **9-59,** this reaction may be looked upon as a combination of $ArN{=}O$ and $ArNH_2$. However, when the reducing agent was $HOCH_2CH_2ONa$, it was shown that azoxy compounds were intermediates.[193] Nitroso compounds may be reduced to azo compounds with $LiAlH_4$.

OS **III,** 103.

9-61 Reduction of nitro to hydrazo compounds

$$2ArNO_2 \xrightarrow[NaOH]{Zn} Ar{-}NH{-}NH{-}Ar$$

Nitro compounds may be reduced to hydrazo compounds with zinc and sodium hydroxide, or electrolytically, or with $LiAlH_4$ mixed with a metal chloride such as $TiCl_4$ or VCl_3.[194] The reduction has also been accomplished with hydrazine hydrate and Raney nickel.[195]

Reactions in Which an Organic Substrate Is Both Oxidized and Reduced. Some reactions which belong in this category have been considered in earlier chapters. Among these are the Tollens condensation (reaction **6-44,** p. 701), the benzil-benzilic acid rearrangement (reaction **8-6,** p. 803), and the Wallach rearrangement (reaction **8-33,** p. 851).

9-62 The Cannizzaro reaction

$$2ArCHO \xrightarrow{NaOH} ArCH_2OH + ArCOO^-$$

Aromatic aldehydes, and aliphatic ones with no α hydrogen, give the *Cannizzaro reaction* when treated with NaOH or other strong bases.[196] In this reaction one molecule of aldehyde oxidizes another to the acid and is itself reduced to the primary alcohol. Aldehydes with an α hydrogen do not give the reaction, because when these compounds are treated with base, the aldol condensation (reaction **6-39,** p. 692) is much faster. Normally the best yield of acid or alcohol is 50% each, but this can be altered in certain cases. When the aldehyde contains a hydroxide group in the ring, then excess base oxidizes the alcohol formed, and the acid may thus be prepared in high yield (the OH^- is reduced to H_2). On the other hand high yields of alcohol may be obtained from almost any aldehyde by running the reaction in the presence of formaldehyde. In this case the formaldehyde reduces the aldehyde to alcohol and is itself oxidized to formic acid. In such a case, where the oxidant aldehyde differs from the reductant aldehyde, the reaction is called the *crossed Cannizzaro reaction.* The Tollens condensation (reaction

---

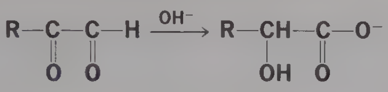
[193] Tadros, Ishak, and Bassili, *J. Chem. Soc.* **1959,** 627.

[194] Olah, *J. Am. Chem. Soc.* **81,** 3165 (1959).

[195] Furst and Moore, *J. Am. Chem. Soc.* **79,** 5492 (1957).

[196] For a review, see Geissman, *Org. Reactions* **2,** 94–113 (1944).

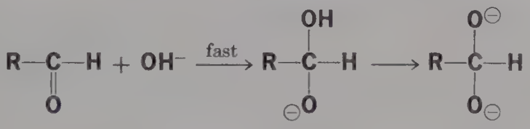
6-44, p. 701) includes a crossed Cannizzaro reaction as its last step. α-Keto aldehydes give internal Cannizzaro reactions:



$$\mathrm{R-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-H \xrightarrow{OH^-} R-\underset{\underset{OH}{|}}{CH}-\underset{\underset{O}{\|}}{C}-O^-}$$

This product is also obtained upon alkaline hydrolysis of compounds of the formula $\mathrm{RCOCHX_2}$. Similar reactions have been performed on γ-keto aldehydes.

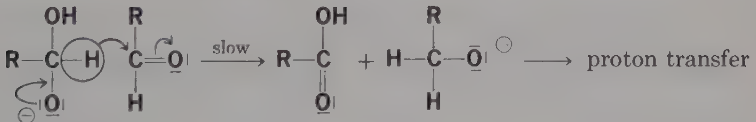
The mechanism of the Cannizzaro reaction involves a hydride shift (an example of mechanism type 2, p. 855). First $\mathrm{OH^-}$ adds to the C=O to give **24,** which may lose a proton in the basic solution to give the diion **25.**



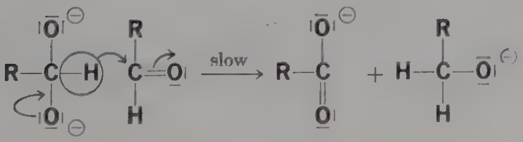
$$\mathrm{R-\underset{\underset{O}{\|}}{C}-H + OH^- \xrightarrow{fast} R-\overset{\overset{OH}{|}}{\underset{\underset{^{\ominus}O}{|}}{C}}-H \longrightarrow R-\overset{\overset{O^{\ominus}}{|}}{\underset{\underset{O^{\ominus}}{|}}{C}}-H}$$

24 **25**

The strong electron-donating character of $\mathrm{O^-}$ greatly facilitates the ability of the aldehydic hydrogen to leave with its electron pair. Of course this effect is even stronger in **25.** When the hydride does leave, it attacks another molecule of aldehyde. The hydride may come from **24** or **25:**



24



25

If the hydride ion comes from **24,** then the final step is a rapid proton transfer. In the other case, the acid salt is formed directly, and the alkoxide ion acquires a proton from the solvent. Evidence for this mechanism is: (1) the reaction may be first order in base and second order in substrate (thus going through **24**) or, at higher base concentrations, second order in each (going through **25**); and (2) when the reaction was run in $\mathrm{D_2O}$, the recovered alcohol contained no α deuterium, indicating that the hydrogen comes from another mole of aldehyde and not from the medium.[197]

OS **I,** 276; **II,** 590; **III,** 538; **IV,** 110.

---

[197] Fredenhagen and Bonhoeffer, *Z. physik. Chem.* **181A**, 379 (1938).

9-63 The Tishchenko reaction

$$2RCHO \xrightarrow{Al(OEt)_3} RCOOCH_2R$$

When aldehydes, with or without α hydrogen, are treated with aluminum ethoxide, one molecule is oxidized and another reduced, as in reaction **9-62,** but here they are found as the ester. The process is called the *Tishchenko reaction.* Crossed Tishchenko reactions are also possible. With more strongly basic alkoxides, such as magnesium or sodium alkoxides, aldehydes with an α hydrogen give the aldol condensation. Like reaction **9-62,** this reaction has a mechanism that involves hydride transfer.

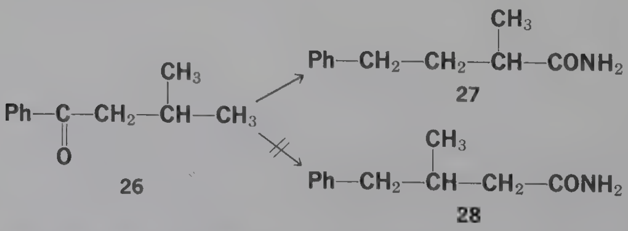
OS **I,** 104.

9-64 The Willgerodt reaction

$$ArCOCH_3 \xrightarrow{(NH_4)_2S_x} ArCH_2CONH_2 + ArCH_2COO^- \quad NH_4^+$$

In the *Willgerodt reaction* a straight- or branched-chain aryl alkyl ketone is converted to the amide and/or the ammonium salt of the acid.[198] The carbonyl group of the product is always at the end of the chain. Thus $ArCOCH_2CH_3$ gives the amide and the salt of $ArCH_2CH_2COOH$, and $ArCOCH_2CH_2CH_3$ gives derivatives of $ArCH_2CH_2CH_2COOH$. However, yields sharply decrease with increasing length of chain. The reaction has also been carried out on vinyl and ethynyl aromatic compounds and on aliphatic ketones, but yields are usually lower in these cases. The use of sulfur and a dry primary or secondary amine (or ammonia) as the reagent is called the *Kindler modification* of the Willgerodt reaction.[199] The product in this case is $Ar(CH_2)_nCSNR_2$, which may be hydrolyzed to the acid.

Though the mechanism of the Willgerodt reaction is not completely known, some conceivable mechanisms may be excluded by the facts which are known. Thus, one might suppose that the alkyl group becomes completely detached from the ring and then attacks it with its other end. However, this possibility is ruled out by experiments such as the following: when isobutyl phenyl ketone (**26**) is subjected to the Willgerodt reaction, the product is **27,** and not **28,** which would arise if the end carbon of the ketone became bonded to the ring in the product:[200]



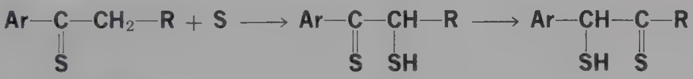
---

[198] For reviews, see Carmack and Spielman, *Org. Reactions* **3,** 83–107 (1946); Wegler, Kühle, and Schäfer, in Foerst, "Newer Methods of Preparative Organic Chemistry," vol. 3, pp. 1–51, Academic Press Inc., New York, 1964 [also appears in *Angew. Chem.* **70,** 351–367 (1958)].

[199] For a review, see Asinger, Schäfer, Halcour, Saus, and Triem, *Angew. Chem. Intern. Ed. Engl.* **3,** 19–28 (1964).

[200] King and McMillan, *J. Am. Chem. Soc.* **68,** 632 (1946).

This also excludes a cyclic-intermediate mechanism, similar to that of the Claisen rearrangement (reaction **8-25**, p. 830). Another important fact is that the reaction is successful for singly branched side chains, such as **26**, but not for doubly branched side chains, as in $PhCOCMe_3$.[200] Still another piece of evidence is that compounds oxygenated along the chain give the same products; thus $PhCOCH_2CH_3$, $PhCH_2COMe$, and $PhCH_2CH_2CHO$ all give $PhCH_2CH_2CONH_2$. All of these facts point to a mechanism consisting of consecutive oxidations and reductions along the chain. Just what form these take is not certain, though a number of theories have been proposed. Initial reduction to the hydrocarbon may be ruled out, since alkylbenzenes do not give the reaction. When acetophenone was treated with butylamine and sulfur, in the Kindler procedure, the imine PhCMe=NBu could be isolated and then converted to the normal product, indicating that the first step of the reaction may well be formation of the imine.[201] The key steps of the mechanism may be of the type



$$\mathrm{Ar{-}\underset{\underset{S}{\|}}{C}{-}CH_2{-}R + S \longrightarrow Ar{-}\underset{\underset{S}{\|}}{C}{-}\underset{\underset{SH}{|}}{CH}{-}R \longrightarrow Ar{-}\underset{\underset{SH}{|}}{CH}{-}\underset{\underset{S}{\|}}{C}{-}R}$$

29

29 may be formed directly from the ketone, or from previously formed imine.

---

[201] Asinger and Halcour, *Monatsh. Chem.* **95**, 24 (1964).

APPENDIX A

Some Notes on the Naming of Organic Compounds

When the beginning student is introduced to the IUPAC[1] rules for the naming of hydrocarbons, usually within the first few weeks of the first-year organic chemistry course, he often marvels at the beauty of the system: each compound has one name; each name refers to one compound; the structural formula can easily be written upon inspection of the name; and, conversely, the name can easily be written upon inspection of the formula. It is not long before the student learns that all is not perfect in the world of organic nomenclature. In this appendix we shall discuss: (1) some general principles concerning nomenclature, (2) some general rules about naming compounds, and (3) rules to cover certain specific cases. It is not our purpose to give a complete guide to organic nomenclature.

Some General Principles. The original version of the rules now known as the IUPAC rules was agreed upon by the International Chemical Congress in Geneva in 1892. The chemists who formulated and approved these rules attempted to put into effect the principle enunciated above: each compound should have one and only one name, and this name should correspond to the structural formula. In order to effect this aim, they discarded all trivial names and all names derived from trivial names. The prohibition extended to trivial group names. Thus were discarded isopropyl (they called it methylethyl), *tert*-butyl (dimethylethyl), etc. However, there were serious obstacles to the attainment of the principle. The structures of many compounds are very complicated, and systematic names would have to be very long (for example, try to write a systematic name for strychnine, p. 168).[2] Very long names may be adequate for some purposes, but if one writes or talks a great deal about a compound, one would rather use a shorter name. This is especially true if one is not a chemist. Thus, people who sell or use the compounds as well as chemists who work with them find it more convenient to say and write DDT, rather than 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane, and mepromate or Miltown, rather than 2-methyl-2-propyl-1,3-propanedioic acid dicarbamate. Of course, many other systematic names are much longer even than these. Another obstacle to total acceptance of the 1892 rules was the existence of many compounds, especially natural products, whose structures were unknown. They had to be given names, which obviously could not be systematic and so had to be trivial. It is true that the trivial names could be discarded once the structures were determined, but by this time they had often become entrenched, and that brings us to the greatest obstacle of all: the fact that most organic chemists simply refused to accept the IUPAC rules when they applied to well-known compounds. Thus the names ethanoic acid (for acetic acid), ethyne (for acetylene), and methylethyl (for isopropyl) were never accepted by the majority of organic chemists.

---

[1] International Union of Pure and Applied Chemistry.

[2] Those intrepid enough to attempt it may find a systematic name for the parent ring system of strychnine in "The Ring Index," 2d ed., p. 1099, American Chemical Society, Washington, D.C., 1960.

In the face of these difficulties the rule codifiers retreated. Revised and extended IUPAC rules were issued in 1930, in 1957, and in 1965.[3] A number of trivial names are now part of the IUPAC system, among them acetylene (though ethyne is also correct), isopropyl, and *tert*-butyl (also *sec*-butyl, isobutyl, isopentyl, neopentyl, *tert*-pentyl, and isohexyl).

The IUPAC rules represent one of the two most important sources of regularity in the naming of organic compounds for English-speaking chemists. The other source is *Chemical Abstracts,* which has its own body of rules.[4] Fortunately, these rules are largely the same as the IUPAC rules. Where they differ, the *CA* rules are more pragmatic. There is a greater acceptance of common names, and of names derived from common names. *Chemical Abstracts* must, perforce, name many compounds which are not covered by the IUPAC rules. Also, *CA* rules can and do change more often than the IUPAC rules, although such changes are still not very frequent.

We may set down a few principles about correct nomenclature:

1. Most compounds (nearly all) have more than one perfectly correct name, sometimes as many as five or six or even more.[5] It is now recognized that the principle of only one name per compound is unattainable. Thus CH_3COCH_3 is correctly called propanone (IUPAC name), acetone, and dimethyl ketone; and $(CH_3)_3CCOOH$ is correctly called 2,2-dimethylpropanoic acid (IUPAC name), trimethylacetic acid, and pivalic acid. However, not every name which seems to be logical is actually a correct name. Thus, the name α,α-dimethylpropionic acid, which is obtained by the normal procedure of substituting two methyl groups for the hydrogens of propionic acid, is *not* a correct name for pivalic acid, *because it is not used* (see below).
2. The IUPAC name for a compound is always regarded as correct, even if the name is hardly ever used.[6] However, the IUPAC system does not cover all compounds.

---

[3] The 1957 definitive IUPAC rules, which include references to earlier reports of the Commission on Nomenclature of Organic Chemistry, may be found in *J. Am. Chem. Soc.* **82,** 5545 (1960). These rules cover hydrocarbons (pp. 5546–5566), fundamental heterocyclic systems (pp. 5566–5574), and amino acids, steroids, vitamins, and carotenoids (pp. 5575–5584). The same issue of the *Journal of the American Chemical Society* also contains the definitive IUPAC rules for inorganic nomenclature (pp. 5523–5544). Compounds containing functional groups involving O, N, S, Se, Te, and/or halogens are treated in the 1965 IUPAC rules [found in *Pure Appl. Chem.* **11,** 1–248 (1965)], which also cover general nomenclature principles.

[4] These rules are periodically printed in the introduction to the *Chemical Abstracts* subject index, most recently in the index to Volume 56 (1962).

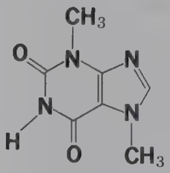
[5] The best place to find several names for a compound is Beilstein (see p. 942). These are in German, but the English equivalents are easily determined in most cases. Another good source (in English) is Heilbron, Cook, Bunbury, and Hey, "Dictionary of Organic Compounds," 5 vols. and suppl., Oxford University Press, New York, 1965.

[6] As indicated earlier, in a very few cases a single compound has two IUPAC names. The vast majority of compounds have one (or no) IUPAC name.

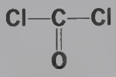
3. Aside from IUPAC names, *the test is usage. If a name is commonly used in the literature, it is correct.*[7] This holds even if the name seems to be illogical (see the next paragraph). As should be apparent from this book, common names are frequently employed.

4. The student should not expect *all* organic names to be logical. Most of them are, but many perfectly acceptable (because they are used) names are not, as the following examples show:

a. Theobromine (**1**) contains no bromine, and phosgene (**2**) contains no phosphorus.



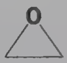
1



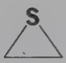
$Cl-\underset{\underset{O}{\|}}{C}-Cl$

2

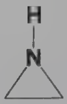
b. Ethylene oxide (**3**) is also called ox*irane,* and **4** is called thi*irane* (logical), but **5** is called az*iridine.*



3



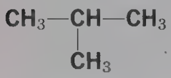
4



5

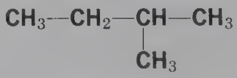
c. Benzhydrol (Ph_2CHOH), azobenzene ($PhN{=}NPh$), and hydrazobenzene ($PhNHNHPh$) all have *two* benzene rings though their names do not show it. *Azo*benzene and benzene*diazo*nium chloride both have *two* nitrogen atoms, although the names would seem to indicate otherwise.

d. Isobutane, isopentane, and isohexane form a logical series, but isooctane is not a member of it.



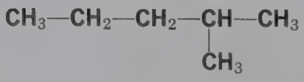
$CH_3-\underset{\underset{CH_3}{|}}{CH}-CH_3$

Isobutane



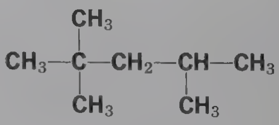
$CH_3-CH_2-\underset{\underset{CH_3}{|}}{CH}-CH_3$

Isopentane



$CH_3-CH_2-CH_2-\underset{\underset{CH_3}{|}}{CH}-CH_3$

Isohexane



$CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-CH_2-\underset{\underset{CH_3}{|}}{CH}-CH_3$

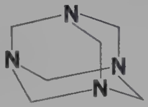
Isooctane

---

[7] This statement is somewhat oversimplified. What is correct usage in one place may not be correct in another. Furthermore, there is no single authority, other than the IUPAC committee on nomenclature (which, of course, deals only with the IUPAC system), to decide which names are correct and which are not. Nevertheless the statement is accepted by a majority of organic chemists.

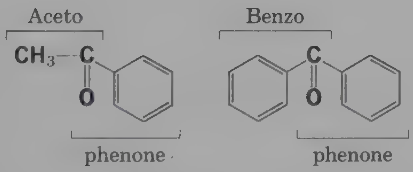
e. The names of most phenols end in the suffix *-ol,* and *ortho*-dihydroxybenzene (catechol) and the meta isomer (resorcinol) follow this rule. But *para*-dihydroxybenzene is called hydroquinone.

f. The hexamethylene radical is $CH_2CH_2CH_2CH_2CH_2CH_2$ (for example, hexamethylene chloride is $ClCH_2CH_2CH_2CH_2CH_2CH_2Cl$), and this is part of a logical sequence of radical names (see p. 918). But compound **6** is called hexamethylenetetramine, although the six carbons are not joined in a chain.



6

g. Perhaps the most important example of illogical usage is the "phenone" system used to name aryl ketones. In most systematic organic names, each part of the name specifies one structural feature, and there is no overlap (that is, a given feature is not denoted by two parts of the name). But in the phenone system (the most common way to name aryl ketones) the carbonyl group is denoted by *both* parts of the name, e.g., in acetophenone and benzophenone,



These examples could be multiplied. Logic therefore is not an infallible guide to the correctness of a name. At the risk of being repetitious, we point out again that *usage determines the correctness of a name.* As we have seen, some illogical names are correct and some logical names are incorrect.

Some General Rules

1. *Substitutive names.* The principle followed in the formation of most organic names is that of substitution on a parent. This is obviously true of the IUPAC system (e.g., 2-methylbutane), but it is also true of many common names (e.g., chloroacetic acid, dimethylacetylene). The parent part of the name consists of a *stem* or *root.* The substituents (which replace hydrogen) are indicated by *prefixes* and/or *suffixes.* If a compound has only one functional group, it is usually indicated by a suffix, except that for some groups there are no suffixes (e.g., halo, nitro, nitroso). Double and triple bonds are always indicated by suffixes, since there are no prefixes for them.[8] If a com-

---

[8] Double and triple bonds are not substituents, since they do not replace hydrogen, but they are treated as such.

pound has two or more functional groups, then the rule is: only one functional group in a molecule may be denoted by a suffix, with two exceptions: (1) if a compound has two or more *identical* functional groups, both may be indicated by the suffix, e.g., 2,3-butanediol; and (2) the syllables "ene" and "yne" are permitted in the suffix along with a suffix denoting another functional group, e.g., 5-hexen-3-yn-2-one. All other functional groups in a molecule must be placed in the prefix, where they are indicated as radicals. Most functional groups can be represented either as suffixes or as prefixes, but not all (see Table 1). The choice of which functional group shall be placed in the suffix, when there are two or more, is determined by an order of precedence which is shown in Table 1 for some common groups. The order is not invariant, but is generally followed. For carboxylic acids there are two suffixes commonly employed. When the suffix "oic acid" is used, the carboxyl carbon is counted as part of the parent, but when the suffix "car-

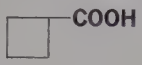
TABLE 1. Some common functional groups, with prefixes and suffixes, listed in approximate order of precedence
Any group on the list takes precedence over a lower group, except for the last eight, which are only prefixes

Group	*Prefix*	*Suffix*
NR_3^+, SR_2^+, etc.		onium (chloride, etc.)
OOH		hydroperoxide
COOH	carboxy	oic acid, carboxylic acid
SO_3H	sulfo	sulfonic acid
COCl, COBr, etc.	chloroformyl, bromoformyl, etc.	oyl chloride, oyl bromide, etc.
$CONH_2$	carbamoyl	oamide
CHO	formyl	aldehyde or al
CN	cyano	nitrile
C=O (RCO, e.g., MeCO)	keto, oxo (acyl, e.g., acetyl)	one
OH (in ROH)	hydroxy	ol
OH (in ArOH)	hydroxy	ol
SH	mercapto	thiol
NH_2	amino	amine
—O— (OR, e.g., OMe)	(alkoxy, e.g., methoxy)	
—S— (SR, e.g., SMe)	(alkylthio, e.g., methylthio)	
—SO— (RSO, e.g., MeSO)	(alkylsulfinyl, e.g., methylsulfinyl)	
$—SO_2—$ (RSO_2, e.g., $MeSO_2$)	(alkylsulfonyl, e.g., methylsulfonyl)	
—N=N—	azo	
NO_2	nitro	
NO	nitroso	
Cl, Br, etc.	chloro, bromo, etc.	

boxylic acid" is employed, the parent is considered to be coupled to the carboxyl carbon, which is hence not counted with the parent, e.g.,

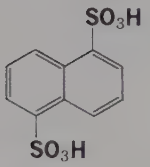
CH_3COOH *eth*anoic acid; but *meth*anecarboxylic acid

Actually, coupling names are never used for such simple carboxylic acids, but they are used in cases where the other type of name is not easy to employ, and for most sulfonic acids, even the simple ones, e.g.,



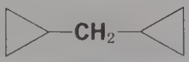
Cyclobutanecarboxylic acid

CH_3SO_3H Methanesulfonic acid



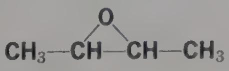
1,5-Naphthalenedisulfonic acid

2. *Choice of a parent.* In cases of ambiguity, the largest or most important part of a molecule is usually chosen as the parent. For example, CH_3CH_2Ph is generally called ethylbenzene rather than phenylethane. However, this principle may be violated when the user of a name is interested in bringing out a particular relationship. A chemist studying the physical properties of a series of compounds $PhCH_2CH_3$, Ph_2CHCH_3, Ph_3CCH_3, may well choose to use the name phenylethane. If one moiety of a compound contains two or more substituents, it is generally the parent, even if it is not the largest or most important part, e.g.,



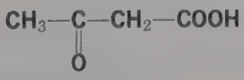
Dicyclopropylmethane

3. *Radicals.* Prefixes in a name are expressed as radicals. There are many more radical names than most students imagine. Almost any part of a structural formula may be named as a radical. The Introduction to the subject index of Volume 56 of *CA*[4] has a list of 900 to 1000 radical names, and these are by no means all. Most radicals are univalent: they are attached to the parent by just one bond (e.g., chloro, methyl, methoxy, acetyl, etc.). However there is a large group of divalent radicals, among them "epoxy" and "oxo," or "keto," e.g.,



$CH_3-\overset{O}{\widehat{CH-CH}}-CH_3$

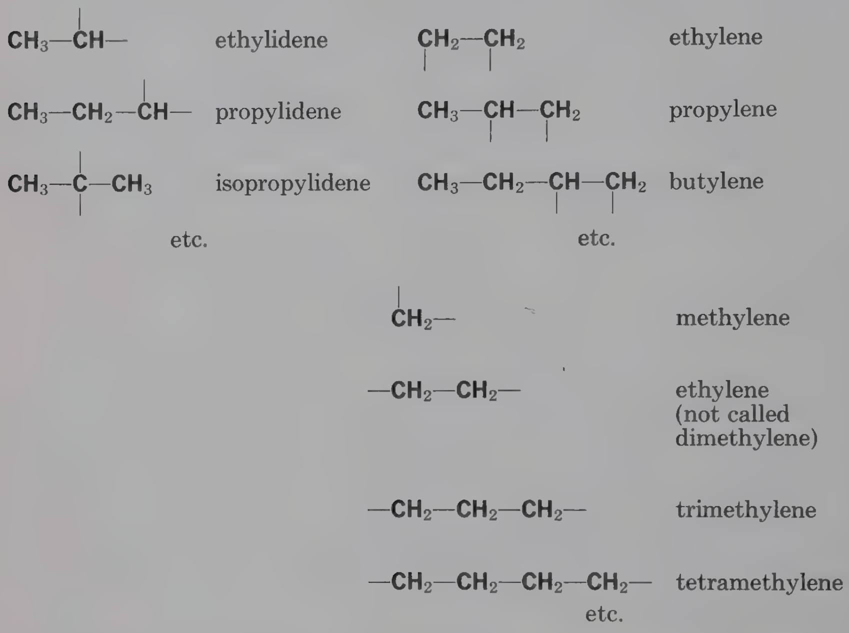
2,3-Epoxybutane



$CH_3-\underset{\overset{\|}{O}}{C}-CH_2-COOH$

3-Oxobutanoic acid
3-Ketobutanoic acid
(More often called by the
common name: acetoacetic acid)

The prefix "oxo" is preferred by both *CA* and the IUPAC, but many chemists continue to use "keto." There are three large groups of divalent radicals derived from alkanes. These have their valences on the same carbon (suffix: *ylidene*); on adjacent carbons (suffix: *ene*); or at the ends of a chain (suffix: *methylene*):

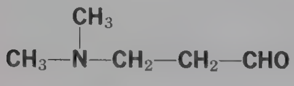


$CH_3-\overset{\vert}{C}H-$	ethylidene	$\underset{\vert}{C}H_2-\underset{\vert}{C}H_2$	ethylene
$CH_3-CH_2-\overset{\vert}{C}H-$	propylidene	$CH_3-\underset{\vert}{C}H-\underset{\vert}{C}H_2$	propylene
$CH_3-\overset{\vert}{\underset{\vert}{C}}-CH_3$	isopropylidene	$CH_3-CH_2-\underset{\vert}{C}H-\underset{\vert}{C}H_2$	butylene
	etc.		etc.

$\overset{\vert}{C}H_2-$	methylene
$-CH_2-CH_2-$	ethylene (not called dimethylene)
$-CH_2-CH_2-CH_2-$	trimethylene
$-CH_2-CH_2-CH_2-CH_2-$	tetramethylene
etc.	

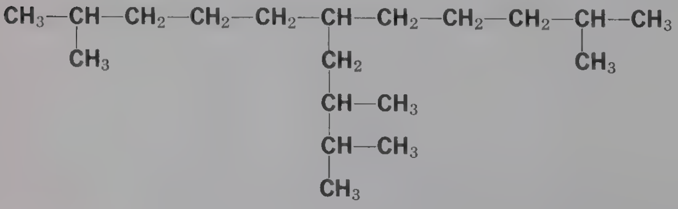
Note that these radicals do not contain internal double bonds. Divalent radicals are most commonly used in radicofunctional names (see p. 920 for examples of usage).

4. *Compound radicals.* The number of possible radical names is greatly extended by the use of compound radicals: radicals substituted on radicals. Use of these permits an enormous degree of flexibility in nomenclature, as illustrated by these examples:



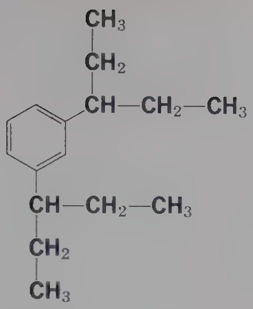
$$CH_3-\overset{\overset{CH_3}{\vert}}{N}-CH_2-CH_2-CHO$$

3-(Dimethylamino)propanal

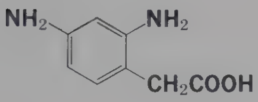


$$CH_3-\underset{\underset{CH_3}{\vert}}{C}H-CH_2-CH_2-CH_2-\underset{\underset{\underset{\underset{\underset{\underset{\underset{CH_3}{\vert}}{CH-CH_3}}{\vert}}{CH-CH_3}}{\vert}}{CH_2}}{\vert}}{C}H-CH_2-CH_2-CH_2-\underset{\underset{CH_3}{\vert}}{C}H-CH_3$$

2,10-Dimethyl-6-(2,3-dimethylbutyl)undecane



meta-Bis(1-ethylpropyl)benzene



(2,4-Diaminophenyl)acetic acid

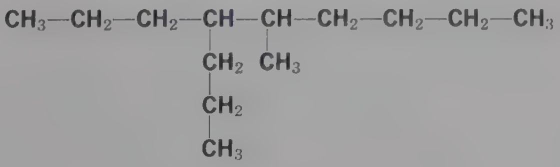
As indicated in the examples, the following customs are followed in the use of compound radicals:

a. The name of the compound radical is usually enclosed in parentheses to avoid possible ambiguity.

b. When two identical compound radicals are attached to one parent, the prefix "bis" is used instead of "di"; and "tris," "tetrakis," "pentakis," etc., instead of "tri," "tetra," "penta," etc.

c. Numbering within a complex radical always begins at the point of attachment to the parent.

5. *Order of radical prefixes.* The IUPAC system allows two methods of assigning prefix order: the groups may be cited in order of "increasing complexity" or in alphabetical order. The increasing-complexity order would have methyl cited before ethyl, etc., but in many cases it is not easy to determine the order of complexity, and the IUPAC rules get down to very detailed cases.[3] *Chemical Abstracts* favors alphabetical order, and on the whole this procedure seems better because it is much easier to apply. In alphabetical order numerical prefixes are not considered. Thus, tri*e*thyl is cited before *m*ethyl or di*m*ethyl. Note that order of groups along a chain is not part of either system, unless it happens also to be an alphabetical order or an order of increasing complexity. Thus, **7** is 5-methyl-4-propylnonane by either acceptable system, and it would be incorrect to say 4-propyl-5-methylnonane simply because this is the order of groups in the chain. However, the order of citation of radical prefixes is generally not very



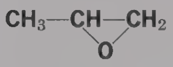
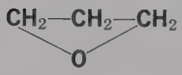
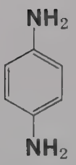
$$CH_3-CH_2-CH_2-\underset{\substack{|\\ CH_2\\ |\\ CH_2\\ |\\ CH_3}}{CH}-\underset{\substack{|\\ CH_3}}{CH}-CH_2-CH_2-CH_2-CH_3$$

7

important except for listings in alphabetical indexes or lists of chemicals in a catalog, and many chemists would regard any order as correct.

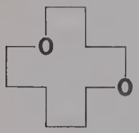
6. *Other types of names.* Some kinds of names which are not of the simple substitutive type are:

a. Radicofunctional names. These are formed from the name of a radical and the name of a functional class, e.g., ethyl bromide, benzoyl chloride, propyl alcohol, diphenyl ketone, etc. Amines are most often named in this manner. Thus CH_3NH_2 is not called methaneamine but methylamine. The "carbinol" names for alcohols (mostly used for tertiary and, to a lesser extent, for secondary and primary alcohols) are radicofunctional names in which the word "carbinol" is substituted for "methanol," e.g., in triphenylcarbinol (Ph_3COH) and allylvinylcarbinol ($CH_2{=}CH{-}CHOH{-}CH_2{-}CH{=}CH_2$). The corresponding halides are sometimes named in a similar manner, e.g., trivinylcarbinyl chloride [$(CH_2{=}CH)_3CCl$]. Some examples of the use of divalent radicals in radicofunctional names are:

$ClCH_2CH_2Cl$	Ethylene chloride
$CH_3{-}CHBr_2$	Ethylidene bromide
 $CH_3{-}\underbrace{CH{-}CH_2}_{O}$	Propylene oxide
 $\underbrace{CH_2{-}CH_2{-}CH_2}_{O}$	Trimethylene oxide
	*para*-Phenylenediamine

Radicofunctional names are very common, especially for well-known compounds. In addition to amines, most simple alcohols, ethers, alkyl halides, acyl halides, anhydrides, mercaptans, sulfides, sulfoxides, sulfones, and peroxides are most often given radicofunctional names.

b. Replacement names. In substitutive names the substituent replaces hydrogen. In *replacement names* it replaces carbon (sometimes oxygen). Where CH_2 is replaced by NH, O, or S, the prefixes *aza, oxa,* and *thia* are used respectively, e.g.,

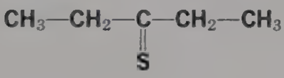
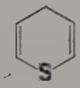
$CH_3{-}CH_2{-}NH{-}CH_2{-}CH_2{-}CH_3$	3-Azahexane (more commonly called ethylpropylamine)
$CH_3{-}S{-}CH_2{-}CH_2{-}S{-}CH_2{-}CH_3$	2,5-Dithiaheptane
	1,6-Dioxacyclododecane

Other hetero atoms are given similar prefixes, e.g.,

Se(II)	selena	**Si**(IV)	sila
P(III)	phospha	**Ge**(IV)	germa
Sn(IV)	stanna	**Hg**(II)	mercura

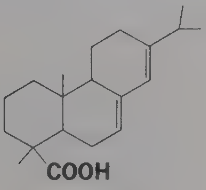
The system is called the *Hantzsch-Widman* system, or the "*a*" *nomenclature,* since each prefix ends in "a." The Roman numeral indicates the oxidation state (for oxa, thia, and aza, these are of course II, II, and III, respectively). When an "a" prefix is used in a name, all other substituents are treated exactly as if the hetero atom were replaced by CH_2.

The use of "thio" for replacement of oxygen by sulfur affords other examples of replacement names:

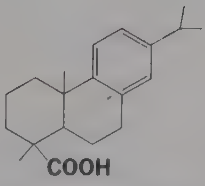
PhSH	Thiophenol
CH_3SH	Methanethiol
 $CH_3-CH_2-\underset{\underset{S}{\Vert}}{C}-CH_2-CH_3$	3-Pentanethione
	Thiopyran

c. Additive names signify addition between molecules and/or atoms rather than substitution. Many of the radicofunctional names involving divalent radicals (p. 920) are additive names, e.g., ethylene bromide, styrene oxide, etc.

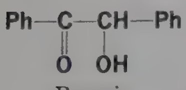
d. Subtractive names. Some prefixes and suffixes signify that something has been *removed* from the parent. The suffixes "ene" and "yne" are actually of this nature. The prefix "dehydro" means lack of two hydrogens, "deoxy" usually signifies replacement of OH by H, and "nor" means lack of a methyl group, e.g.,



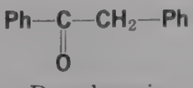
Abietic acid



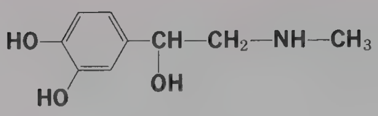
Dehydroabietic acid


$Ph-\underset{\underset{O}{\Vert}}{C}-\underset{\underset{OH}{|}}{CH}-Ph$

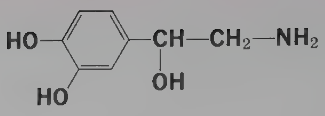
Benzoin


$Ph-\underset{\underset{O}{\Vert}}{C}-CH_2-Ph$

Deoxybenzoin

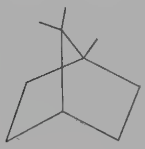


Epinephrene

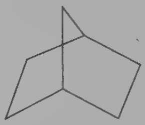


Norepinephrene

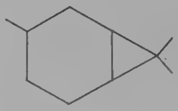
When a compound lacks two or more identical groups, it is customary to use the prefixes bis, tris, etc., rather than di, tri, etc. However, these prefixes are omitted in the cases of norbornane, norcarane, and norpinane, each of which lacks three methyl groups.



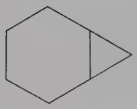
Bornane



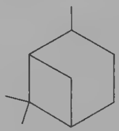
Norbornane



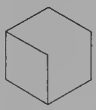
Carane



Norcarane



Pinane

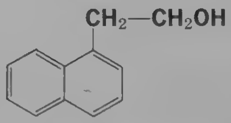


Norpinane

e. Conjugative names. A few names are formed by placing together the names of two molecules, which are joined directly, or through another group, e.g.,

Ph—N=N—CH_3

Benzeneazomethane



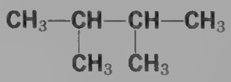
α-Naphthyleneethanol

The molecules are connected by loss of hydrogen from each.

f. Replicate names. The prefix "bi" before a radical name or a parent name indicates that the compound is made up entirely of two such moieties, e.g.,

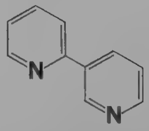
Ph—Ph

Biphenyl



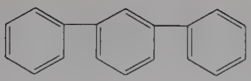
$$\underset{\displaystyle CH_3}{\overset{}{CH_3{-}CH}}{-}\underset{\displaystyle CH_3}{CH}{-}CH_3$$

Biisopropyl

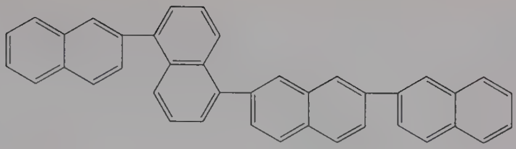


2,3′-Bipyridine

The system is extended to "ter," "quater," etc. (though, strictly speaking, we do not have three or four identical radicals here), e.g.,



meta-Terphenyl

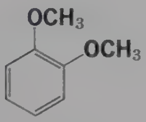


2,1′:5′,2″:7″,2‴-quaternaphthyl

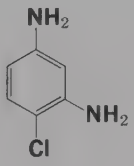
g. Fusion names are considered on page 926.

h. Trivial names are legion, but of course there is no system. The structures which correspond to names like aspirin, vitamin C, carotene, saccharin, thujene, lysergic acid, chrysene, etc., must be individually learned.

7. *Like treatment of like things.* An important principle in all systems is that like groups are to be treated alike. Thus $PhCH_2Ph$ could not be called benzylbenzene, but must be named diphenylmethane. Similarly, **8** would not be called *ortho*-methoxyanisole, but could be called *ortho*-dimethoxybenzene (it is more commonly called veratrole). It is because of this rule that benzene rings containing two like groups and one unlike group are always named using the unlike group as the principal function, e.g., **9** is 2,4-diaminochlorobenzene and not something like 3-amino-6-chloroaniline. It is also because of this rule that replicate names (p. 923) are used for compounds like biphenyl, since otherwise we might have to call this compound phenylbenzene. Incidentally, the name "benzophenone," besides being illogical (p. 915), also violates this rule.



8



9

8. *One word versus two.* There is a very simple rule which covers what otherwise might be the vexing question of when to run parts of a name together and when to separate them. The rule is: if the latter part of the name is the name of an actual compound, the prefix is run into it; if not, it stands alone. For example, there is such a compound as benzene. Therefore chlorobenzene is one word. But there is no such compound as "ketone," so that diphenyl ketone is two words. Amines are apparent exceptions. There is no such compound as "amine," but methylamine is one word. In this case the word "amine" is regarded as a contraction of "ammonia," and of course there is such a compound.

9. Some indexes of chemical names list compounds in simple alphabetical order (especially commercial catalogs), but most do not. These indexes, of which the *CA* index is the most important, *invert* many names, preferring to list them at what is considered to be the most important part of the name,

rather than at the beginning. For example, a strict alphabetical listing of certain phenathrene derivatives would be (omitting position numbers):

Diethylphenanthrene
Dimethylphenanthrene
Ethylphenanthrene
Methylphenanthrene
Phenanthrene
Trimethylphenanthrene

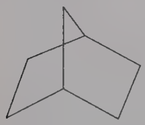
Thus the names would be scattered all over the index. *Chemical Abstracts* would list these names this way:

Phenanthrene
Phenanthrene, diethyl-
Phenanthrene, dimethyl-
Phenanthrene, ethyl-
Phenanthrene, methyl-
Phenanthrene, trimethyl-

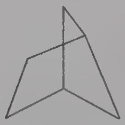
The names would therefore be found close together. Obviously, the user of such a list must be familiar with the method of listing.

Certain Specific Cases. Most of the cases we shall consider involve cyclic compounds.[9]

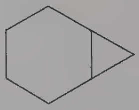
1. *Bicyclic and polycyclic compounds.* Bridged bicyclic compounds are named by the *von Baeyer system.* These compounds consist of two carbon atoms (the *bridgeheads*), which are connected by three separate pathways, called *bridges.* The prefix "bicyclo" is used; the parent is the name corresponding to the total number of carbon atoms in the *ring system* (substituent carbon atoms are not counted); and the number of carbon atoms in each of the three bridges (but not counting the bridgehead carbons) is given, in descending order. Examples are:[10]



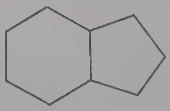
Bicyclo[2.2.1]heptane
(Norbornane)



Bicyclo[2.1.1]hexane



Bicyclo[4.1.0]heptane
(Norcarane)



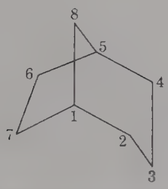
Bicyclo[4.3.0]nonane
(Indane)

---

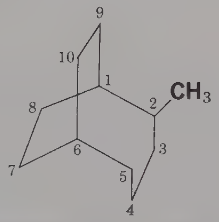
[9] For names of and literature references to thousands of known ring systems, carbocyclic and heterocyclic, simple, fused, spiro, and bridged, see Patterson, Capell, and Walker, "The Ring Index," American Chemical Society, Washington, D.C., 2d ed., 1960; Suppl. I, 1963 (covers 1957–1959); Suppl. II, 1964 (covers 1960–1961); Suppl. III, 1965 (covers 1962–1963).

[10] For additional examples, see page 118.

Note that one of the numbers within the brackets may be zero, but not two. When there is a zero, the compound is called a fused bicyclic system (see the next section). The numbering begins at a bridgehead and proceeds to the other bridgehead by the *longest* path, and then back to the first bridgehead by the second longest path. The shortest bridge is then numbered starting from the first bridgehead, e.g.,

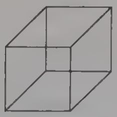


Bicyclo[3.2.1]octane



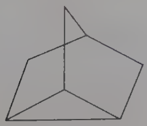
2-Methylbicyclo[4.2.2]decane

The von Baeyer system is also used for bridged compounds of more than two rings, the prefixes being "tricyclo," "tetracyclo," etc. Therefore, it is necessary to know how many rings the system possesses. This number is not always so easy to determine (by inspection) as one might suppose. For example, how many rings has cubane? Fortunately, there is a simple, infallible way to determine the number. One simply ascertains how many scissions are required to convert the system into an open-chain compound.

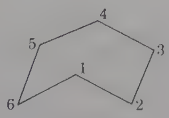


Cubane

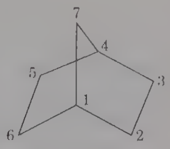
For cubane the number is five; hence it is pentacyclic. Once the number of rings is known, the next step is to determine the "main ring" and the "main bridge," which, of course, form a bicyclic system. The main ring is chosen so as to contain as many carbon atoms as possible, so long as two of them can serve as bridgeheads for the main bridge, which, in case there are two or more possibilities, should be as long as possible. The first three numbers inside the brackets are determined as before, and additional numbers (with superscripts as locants) are used for the additional ring closures. The process may be illustrated for compound **10**. The largest ring contains six carbons (numbered 1 to 6). There is a bridge from C_2 to C_6, but the one from C_1 to C_4 is longer and is hence the main bridge. The resulting bicyclic notation



10

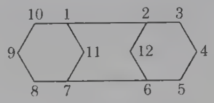


Main ring



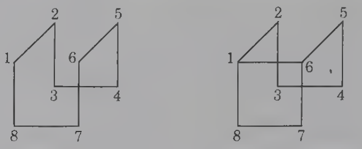
Main ring and main bridge

would be [2.2.1]. The additional ring closure (C_2 to C_6) contains no carbons, and is denoted $0^{2,6}$, so that the complete name of **10** is tricyclo[2.2.1.$0^{2,6}$]heptane. Another example is compound **11**. The main ring is ten-membered



11

(numbered 1 to 10), and the main bridge (C_1 to C_7) has one additional carbon atom, so that the bicyclic notation would be [5.3.1]. The additional bridge contains one carbon atom (from C_2 to C_6), so **11** is named tricyclo[5.3.1.$1^{2,6}$]dodecane. Finally we may look at cubane.[11] Despite appearances, all eight carbon atoms can be put into the main ring. The main bridge (C_1 to C_6) therefore contains no carbons, and the bicyclic notation is [4.2.0]:

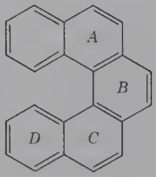


Main ring

Main ring and main bridge

To complete the structure, three more connections are made (C_2 to C_5, C_3 to C_8, and C_4 to C_7), and the systematic name is pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane.

2. *Fused polycyclic compounds.* Many fused aromatic ring systems have trivial names. The 1957 IUPAC rules recognize 35 such names. For other systems, a *fusion name* is used. In such a name one part of the system is recognized as a parent, and the rest, considered to be fused to the parent, is given a prefix, usually ending in "o." An example is dibenzophenanthrene (**12**). The parent is phenanthrene (rings *A, B, C*). Since the rings fused to

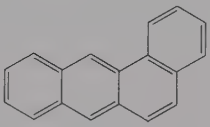


12

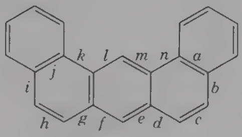
the parent are benzene rings, the prefix "benzo" is used. Other systems may also be used as prefixes, e.g., "naphtho" for naphthalene, "anthra" for anthracene, etc., and even "cyclopenta" for cyclopentane, etc., it being understood that such rings possess the maximum possible number of noncumulative double bonds. It is apparent that **12** could also be named naphthophenanthrene (with rings *B, C,* and *D* constituting the phenanthrene moiety), but the rule is that the attached rings must be as simple as possible, and benzo is simpler than naphtho, even though there must be two benzo rings and only one naphtho. Compound **12** could not be called dinaphthobenzene, since the parent must contain as many rings as possible, provided it has a trivial name. In case the name of the parent starts with a vowel, the "o" is usually elided, e.g., benzanthracene (**13**). If necessary, the position of the attached ring (or rings) is noted by *letters* (not numbers) in brackets, which are assigned to the parent system beginning with *a* for the side 1,2, *b* for 2,3, and continuing around the periphery of the system. Thus **14** is dibenz[*a*,*j*]anthracene.[12] It should be noted that the numbering of the fused compound (dibenzathracene in this case) does not correspond to the numbering of either the original parent or of the rings fused to it. That is, anthracene is given its normal numbering in order to be able to assign the letters *a*, *b*, *c*, etc., but dibenzanthracene is completely renumbered for the purpose of locating substituents on it.

---

[11] For additional examples, see page 118.

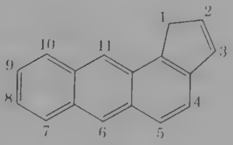


13



14

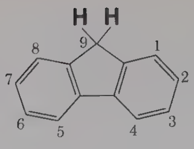
Where just one saturated carbon atom prevents a system from being completely aromatic, the position of this atom is denoted by *H*. The additional hydrogen is called "indicated hydrogen." Thus, **15** is called 1*H*-cyclopent[*a*]anthracene. Indicated hydrogen can be used to distinguish isomers such as **16** and **17**. In this case, **16** is so common that it is generally called



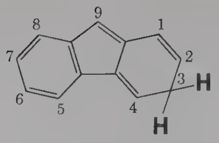
15

---

[12] In some cases it is necessary to provide locants for the attached ring, as well as for the parent. The handling of this situation is shown on page 930.

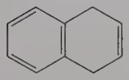


16
9*H*-Fluorene

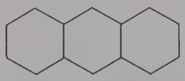


17
3*H*-Fluorene

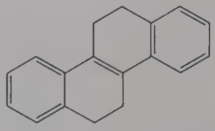
fluorene, without the notation 9*H*. Where fused ring systems are not completely aromatic, "hydro" prefixes are used, e.g.,



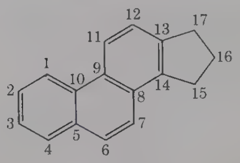
1,4-Dihydronaphthalene



Perhydroanthracene



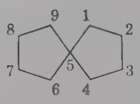
5,6,11,12-Tetrahydrochrysene



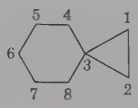
18
16,17-Dihydro-15*H*-cyclopenta[*a*]phenanthrene

Note that **18**, which has the steroid skeleton, is numbered as a steroid.[13]

3. *Spiro compounds.* A spiro compound has one atom which is the only atom common to two rings. Simple spiro compounds are given the prefix "spiro," a suffix corresponding to the total number of carbons, and brackets containing the number of carbon atoms in each ring (not counting the spiro atom), e.g.,



Spiro[4.4]nonane



Spiro[2.5]octane

In contrast to the custom with bridged systems, the numbers within the brackets are in *ascending order.* Numbering begins in the smaller ring, at the position adjacent to the spiro atom, and continues as shown.[14]

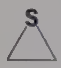
4. *Heterocyclic compounds.* Any monocyclic heterocyclic ring, up to 10-membered, can be very simply named by an extension of the "a" nomenclature discussed on page 921. The system applies to saturated or unsaturated

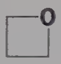
---

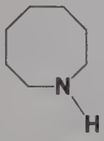
[13] For further rules concerning fused systems, including numbering rules, see the 1957 IUPAC rules (Ref. 3).

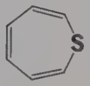
[14] For further rules concerning spiro compounds, see the 1957 IUPAC rules (Ref. 3).

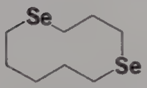
rings, containing one or more hetero atoms, the same or different. The hetero atoms are indicated by prefixes such as aza, oxa, etc., and the *size of the ring* is indicated by a suffix, shown in Table 2. In most cases the "a" is elided. Examples are:

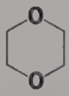

Thiirane

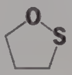

Oxetane


Perhydroazocine

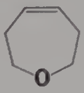

Thiepin


1,5-Diselenecane


1,4-Dioxane


1,2-Oxathiolane

The syllables in Table 2 (for rings of three, four, and seven to ten members) were not chosen at random, but as follows: *ir* from *tri*, *et* from t*et*ra, *ep* from h*ep*ta, *oc* from *oc*ta, *on* from n*on*a, and *ec* from d*ec*a. Where unsaturation is present, but not complete, "hydro" prefixes and indicated hydrogen are used, as appropriate, e.g.,


2,3,6,7-Tetrahydrooxepin

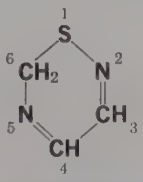
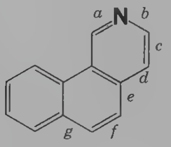

6*H*-1,2,5-Thiadiazine

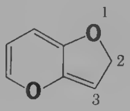
TABLE 2. Suffixes used for the naming of heterocyclic rings
"Unsaturated" rings are understood to contain the maximum number of noncumulative double bonds, the hetero atoms having the normal valences. For saturated N-containing rings of six to ten members, the unsaturated names are used, with the prefix "perhydro"

Number of members in the ring	*N-Containing rings*		*Non-N-containing rings*	
	"Unsaturated"	*Saturated*	*"Unsaturated"*	*Saturated*
3	irine	iridine	irene	irane
4	ete	etidine	ete	etane
5	ole	olidine	ole	olane
6	ine		in	ane
7	epine		epin	epane
8	ocine		ocin	ocane
9	onine		onin	onane
10	ecine		ecin	ecane

Numbering begins with a hetero atom. If there is more than one hetero atom, the order is O, S, Se, Te, N, P, As, Sb, Bi, Si, Ge, Sn, Pb, B, Hg. Heterocyclic rings larger than 10-membered can be named by the regular Hantzsch-Widman system (see p. 920 for an example). Despite the simplicity of the system, many heterocyclic compounds are most often referred to by trivial names. The 1957 IUPAC rules sanction 61 of these, most of which can be used as the basis of fusion "o" names, e.g.,

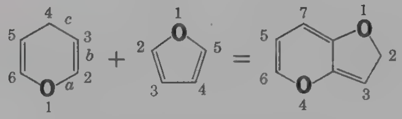


19
Benz[*h*]isoquinoline

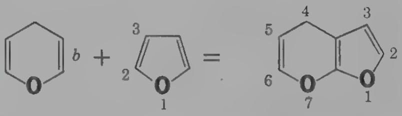


2*H*-Furo[3,2-*b*]pyran

The former example illustrates the principle that a heterocyclic parent is preferred to a carbocyclic one. Thus the compound is not called pyridonaphthalene. The latter example illustrates two principles. The [3,2-*b*] indicates that the fusion is between the *b* side of the pyran and the side containing the 2 and 3 positions of the furan:



The numbering is 3,2 rather than 2,3 because the 3-position of the furan is on the *lower* end (the *a* end) of the *b* side of the pyran. The opposite type of fusion would give:



4*H*-Furo[2,3-*b*]pyran

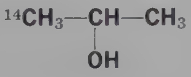
The other principle is the one already mentioned, that the numbering of the fused compound is different from that of either component. For rules governing numbering, see the 1957 IUPAC rules.[3]

5. *Isotopically labeled compounds.* Compounds containing deuterium are given the letter *d,* with a subscript indicating how many, and locant numbers if necessary. The letter and accompanying subscripts and locants are placed after that part of the name designating the hydrogens which are replaced.

Some examples are:

$CDCl_3$	chloroform-*d*
C_6D_6	benzene-d_6
C_6HD_5	benzene-d_5
C_6H_5OD	phenol-*d*
p-DC_6H_4OH	phen-*p*-*d*-ol
CD_3OCD_3	(methyl ether)-d_6
CH_3OCD_3	(methyl ether)-1,1,1-d_3

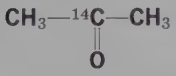
Tritium compounds are named in a similar manner, with *t* instead of *d*. Other labeled compounds are named by an extension of this system, as illustrated in these examples:



$$^{14}CH_3-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_3$$

2-propanol-1-^{14}C

$Ph^{15}NH_2$ aniline-^{15}N



$$CH_3-\underset{\displaystyle O}{\underset{\|}{^{14}C}}-CH_3$$

acetone-2-^{14}C

6. For nomenclature of stereoisomers, see Chapter 4 (pp. 72, 83–84, 88–90, 94–95, and 100).

APPENDIX B

The Literature of Organic Chemistry

All discoveries made in the laboratory must be published somewhere if the information is to be made generally available. A new experimental result which is not published might as well not have been obtained, insofar as it benefits the entire chemical world. The total corpus of chemical knowledge (called *the literature*) is located on the combined shelves of all the chemical libraries in the world. If anyone wishes to learn whether the answer to any chemical question is known, and, if so, what the answer is, he has only to turn to the contents of these shelves. Indeed the very expressions "is known," "has been done," etc., really mean "has been published." To the uninitiated, the contents of the shelves may appear formidably large, but fortunately the process of extracting information from the literature of organic chemistry is usually not difficult, and often not even time-consuming. In this appendix we shall examine the literature of organic chemistry, confining our attention chiefly to the results of laboratory work, rather than those of industrial organic chemistry.[1] The literature may be divided into two broad categories: *primary sources* and *secondary sources.* A primary source publishes the original results of laboratory investigations. Books, indexes, and other publications which cover material which has previously been published in primary sources may be called secondary sources. It is because of the excellence of the secondary sources in the field of organic chemistry (especially *Chemical Abstracts* and Beilstein) that literature searching is comparatively not difficult. The two chief kinds of primary source are journals and patents. There are several types of secondary source.

PRIMARY SOURCES

Journals. For the last hundred years, nearly all new work in organic chemistry (except for that which has been disclosed in patents) has been published in journals. There are thousands of journals which publish chemical papers, in many countries and in many languages. Most are published by chemical and other scientific societies, but some are published by private companies. Some print papers covering all fields of science; some are restricted to chemistry; some to organic chemistry; and there are a few that are still more specialized. Fortunately for the sanity of organic chemists, the vast majority of important papers in "pure" organic chemistry (as opposed to "applied") are published in relatively few journals, perhaps fifty or fewer. Of course, this is still a large number (and it is growing all the time), especially since some are published weekly and some semimonthly, but it is considerably smaller than the total number of journals (perhaps as high as 10,000) which publish chemical articles.

---

[1] There are two excellent monographs on the subject of chemical literature: Crane, Patterson, and Marr, "A Guide to the Literature of Chemistry," 2d ed., John Wiley & Sons, Inc., New York, 1957, and Mellon, "Chemical Publications," 4th ed., McGraw-Hill Book Company, New York, 1965.

In addition to ordinary papers, there are two other types of publications in which original work is reported: *notes* and *communications.* A note is a brief paper, published without a summary (most papers are published with summaries or abstracts prepared by the author). Otherwise, a note is similar to a paper. In recent years, the use of notes has been declining, and some journals no longer publish them. Communications (also called *letters*) are also brief and also without summaries. However, they differ from notes and papers in three respects:

1. They are brief, not because the work is of small scope, but because they are condensed. Usually they include only the most important experimental details, or none at all.
2. They are of immediate significance. Journals which publish communications make every effort to have them appear as soon as possible after they are received. Some papers and notes are of great importance, and some are of lesser importance; but all communications are supposed to be of high importance.
3. Communications are preliminary reports, and the material in them may be republished as papers or notes at a later date, in contrast to the material in papers and notes, which cannot be republished.

Although papers (we use the term in its general sense, to cover notes and communications also) are published in many languages, the English-speaking chemist is in a fairly fortunate position. At the present time, about half of the important papers in organic chemistry are published in English. Not only are American, British, and British Commonwealth journals published almost entirely in English, but so are many others around the world. There are predominantly English-language journals published in Japan, Czechoslovakia, Sweden, the Netherlands, Israel, and other countries. Sometimes articles published in other languages have summaries, or at least titles, printed in English also. Furthermore, the second most important language (in terms of the number of organic chemical papers published) is Russian, and most of these papers are available in English translation, though in most cases 10 months to a year later. A considerable number of important papers are published in German and French, and these are generally not available in translation, so that the organic chemist should have at least a reading knowledge of these languages. An exception is the journal *Angewandte Chemie,* which in 1962 became available in English under the title *Angewandte Chemie International Edition in English.* Of course, a reading knowledge of French and German (especially German) is even more important for the older literature. Before about 1920, more than half of the important chemical papers were in these languages. It must be realized that the original literature is never obsolete. Secondary sources become superseded or outmoded, but nineteenth-century journals may be found in most chemical libraries and are still consulted. Table 1 presents a list of the more important current journals which publish original papers[2] and communications in organic chemistry.[3] Some of them also publish review articles, notes on meetings, book reviews, and other material. Changes in journal title are not

TABLE 1. A list of the more important current journals which publish original papers in organic chemistry, listed in alphabetical order of *Chemical Abstracts* **abbreviations, which are indicated in bold print**
Also indicated are the principal languages (E = English, G = German, F = French, R = Russian, I = Italian); the number of issues per year as of 1967 (exclusive of issues devoted entirely to indexes); and whether the journal primarily publishes papers (including in some cases notes) (P) or communications (C)

Title and year of founding	*Principal languages*	*Papers or communications*	*Issues per year*
1. **Acta Chem**ica **Scand**inavica (1947)	E	P	10
2. **Angew**andte **Chem**ie (1888)[4]	G	C[5]	24
3. Justus Liebigs **Ann**alen der Chemie (also **Ann. Chem.**) (1832)	G	P	10
4. **Ann**ales de **chim**ie **(Paris)** (1789)	F	..[6]	6
5. **Ann**ali di **Chim**ica **(Rome)** (1914)	I	P	12
6. **Ark**iv för **Kemi** (1903)	EG	P	Irreg.
7. **Aust**ralian **J**ournal of **Chem**istry (1948)	E	P	12
8. **Bull**etin of the **Chem**ical **Soc**iety of **Jap**an (1926)	E	PC	12
9. **Bull**etin des **Soc**iétés **Chim**iques **Belg**es (1887)	FE	PC	6
10. **Bull**etin de la **Soc**iété **chim**ique de **Fr**ance (1858)	F	PC	12
11. **Can**adian **J**ournal of **Chem**istry (1929)[7]	EF	P	24
12. **Chem**ische **Ber**ichte (1868)[8]	G	P	12
13. **Chem**ical **Commun**ications (1965)[9]	E	C	24
14. **Chem**istry and **Ind**ustry **(London)** (1923)	E	C	52
15. **Chimia** (1947)	GFE	C	12
16. **Collect**ion of **Czech**oslovak **Chem**ical **Com**munications (1929)	EGR	P	12
17. **Compt**es **rend**us hebdomadaires, **Series C** (1835)[10]	F	C	52
18. **Dokl**ady **Akad**emii **Nauk SSSR** (1922)[4]	R	C	36
19. **Experientia** (1945)	EGF	C	12
20. **Gazz**etta **chim**ica **ital**iana (1871)	I	P	12
21. **Helv**etica **Chim**ica **Acta** (1918)	GF	P	8
22. **Israel J**ournal of **Chem**istry (1963)[11]	E	P	6
23. **Izv**estiya **Akad**emii **Nauk SSSR, Otd**elenie **Khim**icheskikh **Nauk** (1936)[4]	R	PC	12
24. **J**ournal of the **Am**erican **Chem**ical **Soc**iety (1879)	E	PC	26
25. **J**ournal of the **Chem**ical **Soc**iety, Section **B,** Physical-Organic Chemistry (1841)[12]	E	P	12

---

[2] In Table 1 notes are counted as papers.

[3] See the books mentioned in Ref. 1 for longer lists of journals, including discontinued ones.

TABLE 1. Continued

Title and year of founding	Principal languages	Papers or communications	Issues per year
26. Journal of the Chemical Society, Section C, Organic Chemistry (1841)[12]	E	P	24
27. Journal of Heterocylic Chemistry (1964)	E	PC	4
28. Journal of the Indian Chemical Society (1924)	E	P	12
29. Journal of Medicinal Chemistry (1958)	E	P	6
30. Journal of Organometallic Chemistry (1963)	EGF	PC	12
31. Journal of Organic Chemistry (1936)	E	P	12
32. Journal für praktische Chemie (1834)	GE	P	12
33. Monatshefte für Chemie (1870)	G	P	6
34. Nature (1869)	E	C	52
35. Naturwissenschaften (1913)	GE	C	24
36. Pure and Applied Chemistry (1960)	EGF	. .[13]	Irreg.
37. Recueil des travaux chimiques des Pays-Bas (1882)	EGF	PC	11
38. Science (1883)	E	C	52
39. Tetrahedron (1958)	EGF	P	12
40. Tetrahedron Letters (1959)	EGF	C	52
41. Zeitschrift für Naturforschung, teil b (1946)	G	P	12
42. Zhurnal Obshchei Khimii (1869)[4]	R	PC	12
43. Zhurnal Organicheskoi Khimii (1965)[4]	R	PC	12

---

[4] These journals are also available in English translation; see Table 2.

[5] *Angew. Chem.* also publishes review articles.

[6] *Ann. chim. (Paris)*, the oldest chemical journal in the world, founded by, among others, Lavoisier, now publishes primarily theses and review articles.

[7] Former title: Canadian Journal of Research, Section B.

[8] Former title: Berichte der deutschen chemischen Gesellschaft.

[9] Successor to Proceedings of the Chemical Society, which appeared from 1957 to 1964.

[10] Division of *Compt. rend.* into four sections began in 1966. Series C covers all fields of chemistry. The other series cover physics, geology, etc.

[11] Former title: Bulletin of the Research Council of Israel, Section A.

[12] Division of *J. Chem. Soc.* into three sections (Section A: Inorganic, Physical, Theoretical) was begun in 1966.

[13] *Pure Appl. Chem.* publishes IUPAC reports and lectures given at IUPAC meetings.

TABLE 2. Journals from Table 1 which are available in English translation
The numbers are keyed to those of Table 1. The year of first translation is given in parentheses

2. Angewandte Chemie International Edition in English (1962)
18. Proceedings of the Academy of Sciences of the USSR, Chemistry Section [Doklady Chemistry] (1956)
23. Bulletin of the Academy of Sciences of the USSR, Division of Chemical Science (1952)
42. Journal of General Chemistry of the USSR (1949)
43. Soviet Journal of Organic Chemistry (1965)

infrequent. Footnotes to the table indicate the more important of these. However, some of the other journals listed have also undergone title changes.

Patents. In many countries, including the United States, it is possible to patent a new compound or a new method for making a known compound (either laboratory or industrial procedures), so long as the compounds are useful. It comes as a surprise to many to learn that a substantial proportion of the patents granted (on the order of 20 to 30%) are chemical patents. Chemical patents are part of the chemical literature, and both U.S. and foreign patents are regularly abstracted by *Chemical Abstracts*. In addition to learning about the contents of patents from this source, chemists may consult the *Official Gazette* of the U.S. Patent Office, which, published weekly and available in most libraries, lists titles of all patents issued that week. Bound volumes of all U.S. patents are kept in a number of large libraries, including the New York Public Library, which also has an extensive collection of foreign patents. Photocopies of any U.S. patent and of most foreign patents can be obtained at low cost, from the U.S. Patent Office, Washington, D.C., 20231. In addition, *Chemical Abstracts* lists, in the introduction to each issue, instructions for obtaining patents from 24 countries. The same compound or method is often patented in several countries. In such cases, *CA* abstracts only the first patent, but relates the numbers of similar patents in a *patent concordance,* carried in each issue.

Although patents are often very useful to the laboratory chemist, and no literature search is complete which neglects relevant patents, as a rule they are not so reliable as papers. There are two reasons for this:

1. It is in the interest of the inventor to claim as much as possible. Therefore he may, for example, actually have carried out a reaction with ethanol and with 1-propanol, but he will claim all primary alcohols, and perhaps even secondary and tertiary alcohols, glycols, and phenols. An investigator repeating the reaction on an alcohol which the inventor did not use may find that the reaction gives no yield at all. In general, it is safest to duplicate the *actual examples* given, of which most chemical patents contain one or more.
2. Although legally a patent gives an inventor a monopoly, it is up to him to protect any alleged infringements in court, and this may cost a good deal of money. Therefore some patents are written so that certain essential details are concealed or entirely omitted. This practice is not exactly cricket, because a patent is supposed to be a full disclosure, but patent attorneys are generally skilled in the art of writing patents, and procedures given are not always sufficient to duplicate the results.

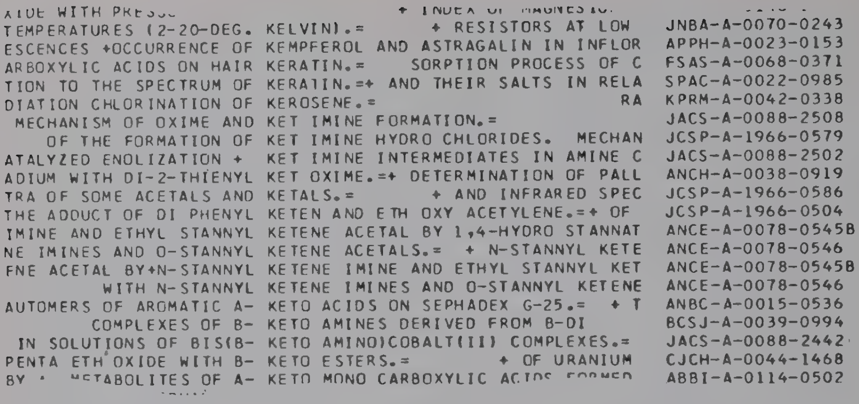
Fortunately, the above statements do not apply to all chemical patents: many make full disclosures and claim only what was actually done. It must also be pointed out that it is not always possible to duplicate the work reported in *every* paper in a journal. In general, however, the laboratory chemist must be more wary of patents than of papers.

SECONDARY SOURCES

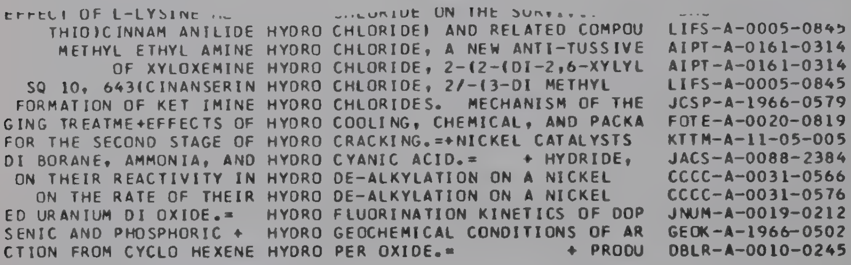
Journal articles and patents contain virtually all of the original work in organic chemistry. However, if this were all—if there were no indexes, guides, review articles, and other secondary sources—the literature would be unusable, because it is so vast that no one could hope to find anything in particular. Fortunately, the secondary sources are excellent. They are of various kinds, and the categories tend to merge. Our classification is somewhat arbitrary.

Listings of Titles. The profusion of original papers is so great that publications which merely list the titles of current papers find much use. Such lists are primarily methods of alerting the chemist to useful papers published in journals which he does not normally read. There are three "title" publications in chemistry. *Current Contents Chemical Sciences,* which began in 1967 and appears weekly, contains the contents pages of all issues of about 160 chemical journals. Russian titles are translated into English, but the titles of German and French papers are given in the original. There is no classification. Each issue contains an author index, which, however, lists only the first-named author of each paper. The author's address is also given, so that one may write for reprints. Useful features of this publication are structural formulas, which are given for compounds mentioned in titles, and a computer-prepared "Permuterm" index, in which alphabetically listed subject words are paired with other words from the same article. *Current Chemical Papers,* published monthly since 1954 by the Chemical Society of London as a successor to *British Abstracts* (p. 941), lists titles of papers from about 300 journals. An advantage over *Current Contents Chemical Sciences* is that the titles are classified in thirteen main sections, with further subclassifications. For example, Section 11 (organic chemistry) is divided into subsections under the titles aliphatic, homocyclic, carbohydrates, etc., and these are subdivided still further. The titles of all papers are given in English, regardless of the original language. There is no author index, and author's addresses are not given.

However, the most useful of the "title" publications is *Chemical Titles,* begun in 1961, which is published by Chemical Abstracts Service and is produced by a computer. This biweekly publication lists titles from about 690 chemical journals, so its coverage is much greater than that of the other two. All of the titles are given in English. The most useful aspect of this publication is the way the titles are given. They are listed in alphabetical order of *every word in the title,* except for such words as "the," "of," "investigation," "synthesis," etc. (each issue contains a list of words prevented from indexing). This means that a title containing seven significant words is listed seven times. Furthermore, at each listing are given the words which immediately precede and follow the alphabetically listed word (called the *keyword*). For example, two short portions of the issue of June 20, 1966, appear thus:



```
XIDE WITH PRES                            + INDEX OF MAGNES
TEMPERATURES (2-20-DEG. KELVIN).=      + RESISTORS AT LOW   JNBA-A-0070-0243
ESCENCES +OCCURRENCE OF KEMPFEROL AND ASTRAGALIN IN INFLOR  APPH-A-0023-0153
ARBOXYLIC ACIDS ON HAIR KERATIN.=    SORPTION PROCESS OF C  FSAS-A-0068-0371
TION TO THE SPECTRUM OF KERATIN.=+ AND THEIR SALTS IN RELA  SPAC-A-0022-0985
DIATION CHLORINATION OF KEROSENE.=                      RA  KPRM-A-0042-0338
 MECHANISM OF OXIME AND KET IMINE FORMATION.=               JACS-A-0088-2508
    OF THE FORMATION OF KET IMINE HYDRO CHLORIDES.  MECHAN  JCSP-A-1966-0579
ATALYZED ENOLIZATION +  KET IMINE INTERMEDIATES IN AMINE C  JACS-A-0088-2502
ADIUM WITH DI-2-THIENYL KET OXIME.=+ DETERMINATION OF PALL  ANCH-A-0038-0919
TRA OF SOME ACETALS AND KETALS.=         + AND INFRARED SPEC  JCSP-A-1966-0586
THE ADDUCT OF DI PHENYL KETEN AND ETH OXY ACETYLENE.=+ OF   JCSP-A-1966-0504
IMINE AND ETHYL STANNYL KETENE ACETAL BY 1,4-HYDRO STANNAT  ANCE-A-0078-0545B
NE IMINES AND O-STANNYL KETENE ACETALS.=  + N-STANNYL KETE  ANCE-A-0078-0546
ENE ACETAL BY+N-STANNYL KETENE IMINE AND ETHYL STANNYL KET  ANCE-A-0078-0545B
         WITH N-STANNYL KETENE IMINES AND O-STANNYL KETENE  ANCE-A-0078-0546
AUTOMERS OF AROMATIC A- KETO ACIDS ON SEPHADEX G-25.=   + T  ANBC-A-0015-0536
        COMPLEXES OF B- KETO AMINES DERIVED FROM B-DI       BCSJ-A-0039-0994
 IN SOLUTIONS OF BIS(B- KETO AMINO)COBALT(III) COMPLEXES.=  JACS-A-0088-2442
PENTA ETH OXIDE WITH B- KETO ESTERS.=           + OF URANIUM  CJCH-A-0044-1468
BY    METABOLITES OF A- KETO MONO CARBOXYLIC ACIDS FORMED   ABBI-A-0114-0502
```



```
EFFECT OF L-LYSINE          CHLORIDE ON THE SUR
    THIO)CINNAM ANILIDE HYDRO CHLORIDE) AND RELATED COMPOU  LIFS-A-0005-0845
     METHYL ETHYL AMINE HYDRO CHLORIDE, A NEW ANTI-TUSSIVE  AIPT-A-0161-0314
         OF XYLOXEMINE HYDRO CHLORIDE, 2-(2-(DI-2,6-XYLYL  AIPT-A-0161-0314
  SQ 10, 643(CINANSERIN HYDRO CHLORIDE, 2/-(3-DI METHYL     LIFS-A-0005-0845
 FORMATION OF KET IMINE HYDRO CHLORIDES.  MECHANISM OF THE  JCSP-A-1966-0579
GING TREATME+EFFECTS OF HYDRO COOLING, CHEMICAL, AND PACKA  FOTE-A-0020-0819
FOR THE SECOND STAGE OF HYDRO CRACKING.=+NICKEL CATALYSTS   KTTM-A-11-05-005
DI BORANE, AMMONIA, AND HYDRO CYANIC ACID.=    + HYDRIDE,   JACS-A-0088-2384
 ON THEIR REACTIVITY IN HYDRO DE-ALKYLATION ON A NICKEL     CCCC-A-0031-0566
   ON THE RATE OF THEIR HYDRO DE-ALKYLATION ON A NICKEL     CCCC-A-0031-0576
ED URANIUM DI OXIDE.=   HYDRO FLUORINATION KINETICS OF DOP  JNUM-A-0019-0212
SENIC AND PHOSPHORIC +  HYDRO GEOCHEMICAL CONDITIONS OF AR  GEOK-A-1966-0502
CTION FROM CYCLO HEXENE HYDRO PER OXIDE.=           + PRODU  DBLR-A-0010-0245
```

Note that a paper entitled "Kinetic Study of the Formation of Ketimine Hydrochlorides. Mechanism of the Hoeben-Hoesch Reaction" is listed under *ketimine* and under *hydrochlorides*. It is also listed under *kinetic, imine, chloride, mechanism, Hoeben, Hoesch,* and *reaction,* making nine listings in all. Certain words (e.g., ketimine, hydrochlorides) are broken into two or more parts, so that additional listings may be obtained. The = sign indicates the end of a title. The value of the index is increased by a "wraparound" feature. If the keyword ends (or begins) the title, what would otherwise be empty space is filled by as many words from the *beginning* (or the end) of the title as will fit. For example, at the entry under the keyword *kerosene,* in the above example, appears the title "Radiation Chlorination of Kerosene." The computer has room in front of the keyword only for DIATION CHLORINATION OF. The remainder of the title, RA, is therefore placed at the end of the line. Where the wraparound feature is used, but the entire title still will not fit, the symbol + is given. This type of listing is called a *Keyword-in-Context* (KWIC) index and is obviously highly useful. For example, if one is interested in thiadiazole, or any of its derivatives, he has but to look it up in *Chemical Titles,* and he will find at once all the papers (in that issue) in which this word appears in the title (the June 20, 1966, issue contains five such listings). The code number given at each entry refers to the source. For example, for the title on ketimines, mentioned above, the number is JCSP-A-1966-0579. The symbols, which are explained in each issue, have the following meanings: JCSP means *J. Chem. Soc. (B);* 1966 is the volume number (actually in this instance 1966 is the year, because this journal has no volume numbers); and 0579 is the page number (579). In the second section of each issue (called the Bibliography) the complete titles and the authors are given. Incidentally, this Bibliography duplicates, for the journals which they both cover, the listings in *Current Contents Chemical Sciences,* since the complete contents of journals are given in order of page number. Each issue of *Chemical Titles* has an author index, but addresses are not given.

Abstracts. Listings of titles are valuable, as far as they go, but they do not tell what is in the paper, beyond the implications carried by the titles. From the earliest days of organic chemistry, abstracts of papers have been widely available, often as sections of journals whose principal interests lay elsewhere.[14] At the present time there are three publications entirely devoted to abstracts covering the whole field of chemistry. For English-speaking chemists the most important of these is *Chemical Abstracts,* and we shall devote most of our attention to it. The other two, *Chemisches Zentralblatt* and *Referativnyi Zhurnal,* will be briefly mentioned later.

Chemical Abstracts, which appears weekly, prints abstracts in English of virtually every paper which contains original work in pure or applied chemistry published anywhere in the world. Approximately 10,000 journals are covered, in many languages. In addition, *CA* publishes abstracts of every U.S., Belgian, British, French, and German patent of chemical interest, as well as of many patents from 20 other countries. *CA* lists and indexes, but does not abstract, review articles and books. The abstracts currently appear in 80 sections, of which sections 21 to 34 are devoted to organic chemistry, under such headings as Noncondensed Aromatic Compounds, Heterocyclic Compounds (One Hetero Atom), Terpenes, etc. Each abstract of a paper begins with a heading which gives (1) the abstract number[15]; (2) the title of the paper; (3) the authors' names as fully as given in the paper; (4) the authors' address; (5) the abbreviated name of the journal (see Table 1)[16]; (6) the volume, issue, page numbers, and year; and (7) the language of the paper. In earlier years *CA* gave the language only if it differed from the language of the journal title. Abstracts of patents begin with the title, inventor and company (if any), patent number, patent class number, date patent issued, date patent applied for, and number of pages in the patent. The body of the abstract is a concise summary of the information in the paper. For certain common journals (for example, *J. Am. Chem. Soc., J. Org. Chem., J. Chem. Soc.*), the author's summary (if there is one) is used in *CA* as it appears in the original paper, with perhaps some editing and additional information. Ordinary abstracts are signed with the name of the abstractor, but these author abstracts are signed with a four-letter code.

---

[14] For example, *Chem. Ind. (London)* and *Angew. Chem.* publish abstracts of papers which appear in other journals. In the past, such journals as *J. Am. Chem. Soc., J. Chem. Soc.,* and *Ber.* also did so.

[15] Beginning in 1967. See p. 941.

[16] These abbreviations are changed from time to time. Therefore the reader may notice inconsistencies.

Each issue of *CA* contains an author index, a patent number index, a patent concordance (see p. 936), and a keyword index, similar to the KWIC index of *Chemical Titles* (p. 937). However, the words in the *CA* keyword index are taken from the titles *and* the texts of the abstracts. No words are given before the keyword, and only two or three after. Of course, these additional words are less necessary here, since the user can immediately refer to the abstract, while in *Chemical Titles* no information is given beyond the title.

Chemical Abstracts is, of course, highly useful for "current awareness"—it allows one to read, in one place, abstracts of virtually all new work in chemistry—though its large size puts a limit on the extent of this type of usefulness. *CA* is even more useful as a repository of chemical information—a place for finding out what was done in the past. This value stems from the excellent indexes, which enable the chemist in most cases quickly to ascertain where information is located. From the time of its founding in 1907 until 1961, *CA* published annual indexes.[16a] Since 1962 there are two volumes published each year, and a separate index is issued for each volume. For each volume there is an index of subjects, authors, formulas, and patent numbers. However, the indexes to each volume become essentially superseded as collective indexes are issued. The first collective indexes are ten-year (decennial) indexes, but the volume of information has made five-year indexes necessary in recent years. Collective indexes so far published are:

Subject	*Author*	*Formula*	*Patent number*
1907–1916	1907–1916		1907–1936
1917–1926	1917–1926		
1927–1936	1927–1936	1920–1946	
1937–1946	1937–1946		1937–1946
1947–1956	1947–1956	1947–1956	1947–1956
1957–1961	1957–1961	1957–1961	1957–1961

Thus, a user of the indexes at this time would consult the collective indexes through 1961, and the semiannual indexes thereafter.

At the beginning of each subject index, annual, semiannual, or collective appears an index of ring systems. This valuable index enables the user to ascertain immediately if any ring system appears in that subject index and under what names. For example, if one wished to determine whether any compounds containing the ring system **19** (p. 930) are reported in the 1957–1961 collective index (even if he did not know the name), he would turn to the listing **6, 6, 6** (since the compound has three rings of 6 members each), under which he would find the sublisting $C_5N—C_6—C_6$ (since one ring contains 5 carbons and a nitrogen while the others are all-carbon), under which is listed the name benzisoquinoline, as well as the names of 9 other systems $C_5N—C_6—C_6$. A search of the subject index under these names will give all references to these ring systems which have appeared in *CA* from 1957 to 1961.

[16a] The subject and formula indexes for 1960 and 1961 are each in two parts: January to June, and July to December.

Before 1967, *CA* used a two-column page, with each column separately numbered. A row of letters from *a* to *h* appeared down the center of the page. These letters are for the guidance of the user. Thus an entry 7337*b* refers to the *b* section of column 7337. In early years superscript numbers, e.g., 4327^5, were used in a similar manner. In very early years these numbers were not printed on the page at all, though they are given in the decennial indexes, so that the user must mentally divide the page into nine parts. Beginning with 1967, abstracts are individually numbered, and column numbers are discarded and replaced with page numbers. Therefore, beginning with 1967, index entries give abstract number rather than column number. The abstract numbers are followed by a letter which serves as a check character to prevent miscopying errors in computer handling. To use the *CA* subject and formula indexes intelligently requires practice, and the student should familiarize himself with representative volumes of these indexes and with the introductory sections to them. The indexes today are as complete as the *CA* staff can make them: about one-half of the total *CA* effort goes into indexes. However, in earlier years, especially before 1920, *CA* indexes were not so complete.

CA uses the *Hill system* for its formula indexes: formulas are listed in order of (1) number of carbon atoms; (2) number of hydrogen atoms; and (3) other elements in alphabetical order. Thus, all C_3 compounds are listed before any C_4 compound; all C_5H_7 compounds before any C_5H_8 compound; $C_7H_{11}Br$ before $C_7H_{11}N$; $C_9H_6N_4S$ before C_9H_6O, etc. Deuterium and tritium are represented by D and T and treated alphabetically, for example, C_2H_5DO after C_2H_5Cl and before C_2H_5F or C_2H_6.

A similar publication in German is *Chemisches Zentralblatt,* which also abstracts papers and patents covering the entire field of chemistry. *Zentralblatt* prints somewhat fewer abstracts than *CA,* but they are likely to be more detailed. The principal value of *Zentralblatt* to English-speaking chemists is the fact that it began in 1830 (under the name *Pharmazeutisches Centralblatt*), and hence covers 1830–1906, which *CA* does not. The Russian abstracting publication *Referativnyi Zhurnal, Khimiya* began publication in 1953. An important source of abstracts in English, now defunct, should be mentioned. From 1871 to 1925, the *Journal of the Chemical Society* published abstracts which covered the important journals of the world. From 1878, the abstracts were separately paged, and usually separately bound. The *Journal of the Society of Chemical Industry* similarly published abstracts in applied chemistry from 1882 to 1925. In 1926 the abstracting services were removed from the journals and combined to form *British Chemical Abstracts* (later *British Chemical and Physiological Abstracts,* and finally *British Abstracts*). In 1953, this publication was terminated, and replaced by *Current Chemical Papers* (p. 937), since the excellence of *Chemical Abstracts* had made its services unnecessary.

Two other publications, though not strictly abstracting publications, should be mentioned here. *Index Chemicus,* begun in 1960 and appearing biweekly, prints structural formulas of all *new* compounds reported in the literature, with formula and author indexes. *Chemical-Biological Activities,* begun in 1964 and published biweekly by Chemical Abstracts Service, presents new data on the biological activity of organic compounds. There are author, formula, and KWIC (see p. 938) indexes.

Compendia and Tables of Information. There are many reference works in organic chemistry which are essentially compilations of data. These books are very useful and often save the research worker a great deal of time. In this section we discuss some of the more important of such works.

1. By far the most outstanding of these compendia is Beilstein's "Handbuch der Organischen Chemie" (in German), usually referred to as *Beilstein.* In this work are listed all of the known organic compounds which were reported in the literature during its period of coverage. For each compound the following data are given: all names, the molecular formula, the structural formula, all methods of preparation (briefly: e.g., "by refluxing 1-butanol with NaBr and sulfuric acid"), physical constants such as melting point, refractive index, etc., other physical properties, chemical properties including reactions, occurrence in nature (that is, which species it was isolated from), biological properties if any, derivatives with melting points, analytical data, and any other information which has been reported in the literature. Equally important, for every piece of information, a reference is given to the original literature. Some compounds are discussed in two or three lines, and others require several pages. The value of such a work should be obvious to all.

For many years a degree of training was required in order to use Beilstein, but the publication of a formula index now makes it fairly easy to use. The first three editions are obsolete. The fourth edition (*vierte Auflage*) covers the literature from its beginnings through 1909. This edition, called *das Hauptwerk,* consists of 27 volumes. The compounds are arranged in order of a system which is too elaborate to discuss fully here.[17] The compounds are divided into three divisions which are further subdivided into "systems":

Division	*Volumes*	*System numbers*
I. Acyclic compounds	1–4	1–449
II. Carbocyclic compounds	5–16	450–2359
III. Heterocyclic compounds	17–27	2360–4720

Das Hauptwerk is still the basis of Beilstein and has not been superseded. The later literature is covered by supplements. The first of these (*erstes Ergänzungswerk*) covers 1910–1919; the second supplement (*zweites Ergänzungswerk*) covers 1920–1929; and the third supplement (*drittes Ergänzungswerk*) covers 1930–1949. The supplements have been arranged to parallel *das Hauptwerk.* The same system is used, so that compounds are treated in the same order, and the same division into volumes is also used. Thus, each supplement contains 27 volumes,[18] and, for example, compounds found in Vol. 3, system number 199, of *das Hauptwerk* will also be found in Vol. 3, system number 199, of each supplement.[19] To make cross-referencing even easier, each supplement gives, for each compound, the page numbers at which the same compound may be found in the earlier books. Thus, on page 545 of Vol. 6 of the third supplement, under the listing phenetole are found the symbols (H 140; E I 80; E II 142) indicating that earlier information on phenetole is given on page 140 of Vol. 6 of *das Hauptwerk,* on page 80 of the first and page 142 of the second supplement. Furthermore, each page of the supplements contains, at the top center, the corresponding page numbers of *das Hauptwerk.* Since the same systematic order is followed in all four series, location of a compound in any one series gives its location in the other three. If a compound is found, for example, in Vol. 5 of *das Hauptwerk,* one has but to note the page number, and scan Vol. 5 of each supplement until that number appears in the top center of the page (of course, the same number may cover several pages). Of course, many compounds are found in only one, two, or three of the series, since a listing appears only if original work on that compound was published during the period covered.

---

[17] A guide to the system is by Huntress, "A Brief Introduction to the Use of *Beilstein's Handbuch der Organischen Chemie,*" 2d ed., John Wiley & Sons, Inc., New York, 1938.

[18] In some cases, to keep the system parallel and to avoid books which are too big or too small, volumes are issued in two or more parts, and, in other cases, two volumes are bound as one.

Volumes 28 and 29 of Beilstein are subject and formula indexes, respectively. The most recent edition of these volumes is part of the second supplement, and it makes the earlier indexes obsolete, since these indexes are collective: they cover *das Hauptwerk* and the first two supplements. For English-speaking chemists (and probably for many German-speaking chemists) the formula index is more convenient. Of course, one must still know some German, for most formula listings contain the names of many isomers. If a compound is found only in *das Hauptwerk,* the index listing is merely the volume and page numbers, for example, **1,** 501. Roman numbers are used to indicate the supplements, for example, **26,** 15, I 5, II 7. Thus the subject and formula indexes lead at once to locations in *das Hauptwerk* and the first two supplements. Locating the compound in the third supplement is then simple (if that volume has already appeared) by the page-number indication mentioned above. However, the most recent edition of Vols. 28 and 29 obviously can contain only compounds which have appeared in the literature before 1930. In order to ascertain if a particular compound, which is not listed in Vol. 28 or 29, is listed in the third supplement, one can follow one of two procedures. Each separately bound portion of each volume of the third supplement has its own subject and formula indexes. If one knows (from an approximate knowledge of the system) in which volume the compound is likely to be found, he can turn to the indexes of that volume, or if he does not mind a little extra labor, he can look in all the indexes. The other procedure is to learn the system—a thing which was done by most organic chemists before the appearance of the original formula index.[17] Even an approximate knowledge of the system often helps. Like *CA*, the formula index of Beilstein uses the Hill system for arrangement of formulas (see p. 941).[20]

---

[19] The third supplement is not yet complete. At this writing Vol. 6 is the latest that has appeared.

[20] The now obsolete formula index to the first supplement (which included *das Hauptwerk*) uses another system, called the *Richter system,* in which formulas are listed according to how many different elements they contain.

There is also a fourth division of Beilstein (systems 4721 to 4877) which covers natural products of uncertain structure: rubbers, sugars, etc. These are treated in Vols. 30 and 31, which do not go beyond 1935 and which are covered in the collective indexes. No supplements to them have appeared.

2. Some years ago a work was announced which was to be the English equivalent of Beilstein: *Elsevier's "Encyclopedia of Organic Chemistry."* Three volumes were published, in more than 15 parts: Vol. 12, bicyclic compounds; Vol. 13, tricyclic compounds; and Vol. 14, tetra- and higher cyclic compounds. These volumes cover many natural products, especially terpenes and steroids. Although the production of the earlier volumes in the series has now been abandoned, these volumes remain valuable.

3. The fourth edition of the "Dictionary of Organic Compounds" (editorial board: Heilbron, Cook, Bunbury, and Hey), 5 vols., Oxford University Press, New York, 1965, contains brief listings of more than 40,000 organic compounds, giving names, structural formulas (in cases where there might be doubt), physical properties and derivatives, with references. For many entries additional data concerning occurrence and biological activity are also given. The arrangement is alphabetical, and there is no index. However, compounds listed under one name are also cross-referenced under other names. The first supplements are dated 1965 and 1966.

4. A multivolume compendium of physical data is Landolt-Börnstein's "Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik, und Technik," 6th ed., Springer-Verlag OHG, Berlin, 1950–. This compendium, which is not yet complete, lists a great deal of data, some of which are of interest to organic chemists, for example, indexes of refraction, heats of combustion, optical rotations, and spectral data. Literature references are given for all data.

5. "The Handbook of Chemistry and Physics," Chemical Rubber Publishing Company, Cleveland, Ohio (fondly called the "rubber handbook"), which is revised annually (46th ed., 1965–1966), is a valuable repository of data quickly found. For organic chemists the most important table is "Physical Constants of Organic Compounds," which lists names, formulas, color, solubilities, and physical properties of thousands of compounds, and which occupies nearly half of the volume. However, there are many other useful tables. A similar work is Lange's "Handbook of Chemistry," 10th ed., McGraw-Hill Book Company, New York, 1966.

6. Dreisbach, "Physical Properties of Chemical Compounds," Advances in Chemistry Series Nos. 15, 22, 29, American Chemical Society, Washington, D.C., 1955–1961, lists many physical properties of more than 1000 organic compounds.

7. Physical properties of thousands of organometallic compounds, with references, are collected in a 1546-page volume: Kaufman, "Handbook of Organometallic Compounds," D. Van Nostrand Company, Inc., Princeton, N.J., 1961.

8. "The Merck Index of Chemicals and Drugs," 7th ed., Merck and Company, Rahway, N.J., 1960, is a good source of information about chemicals of medicinal importance. Many drugs are given three types of name: *chemical name* (which is the name an organic chemist would give it; of

course, there may well be more than one); *generic name,* which must be placed on all containers of the drug; and *trade names,* which are different for each company which markets the drug. For example, the generic name for 1-(4-chlorobenzhydryl)-4-methylpiperazine dihydrochloride is chlorcyclazine hydrochloride. Among the trade names for this drug, which is an antihistamine, are Trihistan, Perazil, and Diparalene. The "Merck Index" is especially valuable because it gives all known names of all three types for each compound, and the names are cross-indexed. The index also gives, for each compound, the structural formula, physical properties, medicinal and other uses, toxicity indications, and references to methods of synthesis.

9. There are two publications which list properties of azeotropic mixtures. Timmermans, "The Physico-Chemical Constants of Binary Systems in Concentrated Solutions," 4 vols., Interscience Publishers, Inc., New York, 1959–1960, with supplements beginning 1965, is by far the more comprehensive. The other is "Azeotropic Data," 2 vols., Advances in Chemistry Series No. 6 and No. 35, American Chemical Society, Washington, D.C., 1952, 1962.

10. Calculated boiling points at many pressures are given for many compounds in Dreisbach, "Pressure-Volume-Temperature Relationships of Organic Compounds," McGraw-Hill Book Company, New York, 1952.

11. A useful source of derivative melting points is "Tables for Identification of Organic Compounds," Chemical Rubber Publishing Company, Cleveland, Ohio, 1960.

12. Thousands of dipole moments, with references, are collected in McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman and Company, San Francisco, 1963.

13. "Tables of Interatomic Distances and Configurations in Molecules and Ions," Special Publication No. 11, London Chemical Society, 1958, and its supplement, Special Publication No. 18, 1965, include bond distances and angles for hundreds of compounds, along with references.

14. "The Ring Index," American Chemical Society, Washington, D.C., 1960, with supplements beginning 1963, lists, in a systematic order, names and formulas of all ring systems in the literature. References are given for each system.

15. A list of review articles, with page numbers, appearing in the major review journals and books (see the next section), may be found in Kharasch, Wolf, and Harrison, "Index to Reviews, Symposia Volumes, and Monographs in Organic Chemistry," Pergamon Press, New York. Three volumes have so far appeared, covering 1940–1960 (pub. 1962); 1961–1962 (pub. 1964); and 1963–1964 (pub. 1966).

16. A number of collections of spectral data are mentioned in Chapter 6.

Reviews. A review article is an intensive survey of a rather narrow field; e.g., the titles of some recent reviews are "Ring Closures with Carbon Monoxide,"[21] "Organic Polyvalent Iodine Compounds,"[22] and "The Strengths of Metal-to-Carbon Bonds."[23] A good review article is of enormous value, because it is a

[21] Falbe, *Angew. Chem. Intern. Ed. Engl.* **5**, 435–446 (1966).

[22] Banks, *Chem. Rev.* **66**, 243–266 (1966).

[23] Skinner, *Advan. Organometal. Chem.* **2**, 49–114 (1964).

thorough survey of all the work done in the field under discussion. Review articles are printed in review journals and in certain books. The most important review journals in organic chemistry (though none except the last is exclusively devoted to organic chemistry) are, with the year of founding, principal languages, and issues per year:

Chemical Reviews (1924)	E	6
Quarterly Reviews (London) (1947)	E	4
Angewandte Chemie (1888)	G	24
and its English translation:		
Angewandte Chemie International Edition in English (1962)	E	12
Uspekhi Khimii (1932)	R	12
and its English translation:		
Russian Chemical Reviews (1960)	E	12
Record of Chemical Progress of the Kresge-Hooker Scientific Library (1939)	E	4
Fortschritte der Chemischen Forschung (1949)	GE	Irreg.
Reviews of Pure and Applied Chemistry (1951)	E	4
Organometallic Chemistry Reviews (1966)	E	4

The *Bull. Soc. chim. France* and *Experientia* also publish occasional review articles.

There are several open-ended serial publications which are similar in contents to the review journals but are published irregularly (seldom more often than once a year) and are hardbound. Some of these publish reviews in all fields of chemistry; some cover only organic chemistry; and some specialize further. The coverage is indicated by the titles. When referring to these references, some chemists treat them as books and some as journals (as does *Chemical Abstracts*). In this book we have followed the latter course. Some of the more important such publications, with *CA* abbreviations, are:

Advances in **Alicyclic Chem**istry
Advances in **Carbohydrate Chem**istry
Advances in **Fluorine Chem**istry
Advances in **Free Radical Chem**istry
Advances in **Heterocyclic Chem**istry
Advances in **Organometallic Chem**istry
Advances in **Organic Chem**istry
Advances in **Photochem**istry
Advances in **Phys**ical-**Org**anic **Chem**istry
Advances in **Protein Chem**istry
Fortschritte der **Chemie org**anischer **Naturstoffe**
Organic **Reactions**
Progress in **Org**anic **Chem**istry
Progress in **Phys**ical-**Org**anic **Chem**istry
Progress in **Stereochem**istry

Survey of Progress in Chemistry
Topics in Phosphorus Chemistry
Topics in Stereochemistry

There are, in addition, a few nonserial books which are essentially collections of unrelated review articles, among them:

Gilman, "Organic Chemistry," 2d ed., 4 vols., John Wiley & Sons, Inc., New York, 1943–1953.
Todd, "Perspectives in Organic Chemistry," Interscience Publishers, Inc., New York, 1956.
"Theoretical Organic Chemistry, The Kekulé Symposium," Butterworth Scientific Publications, London, 1959.

One further type of publication should be mentioned. The "Annual Reports on the Progress of Chemistry," issued every year by the London Chemical Society, contains a good survey of work published in the preceding year. Capon, Perkins, and Rees, "Organic Reaction Mechanisms," Interscience Publishers, Inc., New York, is a publication of a similar nature, whose scope is indicated by the title. This publication is designed to keep the reader currently aware of the latest developments in this area. The first of the annual volumes, covering work published in 1965, appeared in 1966. A similar work, with a different emphasis, is "Annual Surveys of Organometallic Chemistry," by Seyferth and King, American Elsevier Publishing Company, New York, which began appearing in 1965 (covering work published in 1964).

Monographs and Treatises on Specific Areas. Organic chemistry is blessed with a large number of books devoted to a thorough coverage of a specific area. Many of these are essentially very long review articles, differing from ordinary review articles only in size and scope. Some of the books are by a single author, and others have chapters by different authors, but all are carefully planned to cover a specific area. It would not be feasible in this space to give an exhaustive list of such works, and we content ourselves with mentioning some of the more important ones. Others have been referred to in footnotes at appropriate places in the book. In particular, see Chapter 6 for many monographs on physical methods, since these, with one exception, have not been included in the list below.

Amis, "Solvent Effects on Reaction Rates and Mechanisms," Academic Press Inc., New York, 1966.
Banthorpe, "Elimination Reactions," American Elsevier Publishing Company, New York, 1963.
Bartlett, "Nonclassical Ions: Reprints and Commentary," W. A. Benjamin, Inc., New York, 1965.
Brown, "Hydroboration," W. A. Benjamin, Inc. New York, 1962.
Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," American Elsevier Publishing Company, New York, 1963.
Calvert and Pitts, "Photochemistry," John Wiley & Sons, Inc., New York, 1966.
Clar, "Polycyclic Hydrocarbons," 2 vols., Academic Press Inc., New York, 1964.

Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, 1965.

de la Mare and Bolton, "Electrophilic Additions to Unsaturated Systems," American Elsevier Publishing Company, New York, 1966.

de la Mare and Ridd, "Aromatic Substitution—Nitration and Halogenation," Academic Press Inc., New York, 1959.

Elderfield, "Heterocyclic Compounds," 7 vols., John Wiley & Sons, Inc., New York, 1950–1961.

Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, New York, 1962.

Eliel, Allinger, Angyal, and Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, 1965.

Fieser and Fieser, "Steroids," Reinhold Publishing Corporation, New York, 1959.

Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, 1956.

Gilbert, "Sulfonation and Related Reactions," Interscience Publishers, Inc., New York, 1965.

Ginsburg, "Non-Benzenoid Aromatic Compounds," Interscience Publishers, Inc., New York, 1959.

Greenstein and Winitz, "Chemistry of the Amino Acids," 3 vols., John Wiley & Sons, Inc., New York, 1961.

Hanack, "Conformation Theory," Academic Press Inc., New York, 1965.

Hine, "Divalent Carbon," The Ronald Press Company, New York, 1964.

House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, 1965.

Johnson, "Ylide Chemistry," Academic Press Inc., New York, 1966.

Kan, "Organic Photochemistry," McGraw-Hill Book Company, New York, 1966.

Kharasch and Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., Englewood Cliffs, N.J., 1954.

Kirmse, "Carbene Chemistry," Academic Press Inc., New York, 1964.

Manske and Holmes, "The Alkaloids," 9 vols., Academic Press Inc., New York, 1950–1967.

Mayo, "Molecular Rearrangements," 2 vols., Interscience Publishers, Inc., New York, 1963–1964.

Migrdichian, "Organic Synthesis," 2 vols., Reinhold Publishing Corporation, New York, 1957.

Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, 1965.

Muller and Hamer, "1,2 Cycloaddition Reactions," Interscience Publishers, Inc., New York, 1967.

Murray and Williams, "Organic Syntheses with Isotopes," 2 vols., Interscience Publishers, Inc., New York, 1958.

Neckers, "Mechanistic Organic Photochemistry," Reinhold Publishing Corporation, New York, 1967.

Newman, "Steric Effects in Organic Chemistry," John Wiley & Sons, Inc., New York, 1955.

Norman and Taylor, "Electrophilic Substitution in Benzenoid Compounds," American Elsevier Publishing Company, New York, 1965.

Ochiai, "Aromatic Amine Oxides," American Elsevier Publishing Company, New York, 1967.

Olah, "Friedel-Crafts and Related Reactions," 4 vols., Interscience Publishers, Inc., New York, 1963–1965.

Ourisson, Crabbé, and Rodig, "Tetracyclic Triterpenes," Holden-Day, Inc., San Francisco, 1964.

Patai, "Chemistry of the Alkenes," Interscience Publishers, Inc., New York, 1965.

Patai, "Chemistry of Carbonyl Group," Interscience Publishers, Inc., New York, 1965.

Patai, "Chemistry of the Ether Linkage," Interscience Publishers, Inc., New York, 1966.
Pauling, "The Nature of the Chemical Bond," 3d ed., Cornell University Press, Ithaca, N.Y., 1960.
Pimentel and McClellan, "The Hydrogen Bond," W. H. Freeman and Company, San Francisco, 1960.
Pryor, "Free Radicals," McGraw-Hill Book Company, New York, 1966.
Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill Book Company, New York, 1962.
Reid, "Organic Chemistry of Bivalent Sulfur," 5 vols., Chemical Publishing Company, Inc., New York, 1958–1963.
Schroder and Lubke, "The Peptides," 2 vols., Academic Press Inc., New York, 1965–1966.
Simonson, Owen, Barton, and Ross, "The Terpenes," 5 vols., Cambridge University Press, New York, 1947–1957.
Smith, "The Organic Chemistry of Open-chain Nitrogen Compounds," 2 vols., W. A. Benjamin, Inc., New York, 1965–1966.
Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill Book Company, New York, 1965.
Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," The Macmillan Company, New York, 1964.
Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, 1961.
Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Company, New York, 1962.
Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, 1965.
Walling, "Free Radical Reactions," John Wiley & Sons, Inc., New York, 1957.
Weissberger, "The Chemistry of Heterocyclic Compounds," many vols., Interscience Publishers, Inc., New York, 1950–.
Weissberger, "Technique of Organic Chemistry," 11 vols., Interscience Publishers, Inc., New York, 1946–1965.
Wheland, "Resonance in Organic Chemistry," John Wiley & Sons, Inc., New York, 1955.
Wiberg, "Oxidation in Organic Chemistry," 2 vols., Academic Press Inc., New York, 1965–1966.
Zollinger, "Azo and Diazo Chemistry," Interscience Publishers, Inc., New York, 1961.

General Treatises. There are a number of large-scale multivolume treatises which cover the whole field of organic chemistry.

1. An important treatise in English is "Chemistry of Carbon Compounds," edited by Rodd, Elsevier Publishing Company, Amsterdam. The five volumes of this work were issued in ten parts from 1951 to 1962. The organization is not greatly different from that of most textbooks, but the coverage is much broader and deeper. Publication of an enlarged second edition, called "Rodd's Chemistry of Carbon Compounds," edited by Coffey, was begun in 1964.

2. Houben-Weyl's "Methoden der organischen Chemie," Georg Thieme Verlag KG, Stuttgart, is a major treatise in German which is devoted to laboratory methods. The fourth edition, which was begun in 1952 and consists of 16 volumes, some in several parts, is edited by E. Muller. The first four volumes contain general laboratory methods, analytical methods,

physical methods, and general chemical methods. The later volumes are devoted to specific types of compounds, e.g., hydrocarbons, oxygen compounds, nitrogen compounds, etc.

3. A third major treatise is Grignard's "Traité de chimie organique," 23 vols., Masson et Cie, Paris, 1935–1954, in French. The coverage, which is by functional groups, is broad and deep.

Textbooks. There are many excellent textbooks in the field of organic chemistry, of which we list here only a few. Some of these are first-year texts, and some are advanced (advanced texts generally give references; first-year texts do not, though they may give general bibliographies, suggestions for further reading, etc.); some cover the whole field, and others cover reactions, structure, and/or mechanism only. All of the books listed here are not only good textbooks but valuable reference books for graduate students and practicing chemists.

Bordwell, "Organic Chemistry," The Macmillan Company, New York, 1963.

Breslow, "Organic Reaction Mechanisms," W. A. Benjamin, Inc., New York, 1965.

Cram and Hammond, "Organic Chemistry," 2d ed., McGraw-Hill Book Company, New York, 1964.

Ferguson, "Modern Structural Theory of Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N.J., 1963.

Ferguson, "Textbook of Organic Chemistry," 2d ed., D. Van Nostrand Company, Inc., Princeton, N.J., 1965.

Fieser and Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corporation, New York, 1961, and "Topics in Organic Chemistry," Reinhold Publishing Corporation, New York, 1963.

Fuson, "Reactions of Organic Chemistry," John Wiley & Sons, Inc., New York, 1962.

Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, Inc., New York, 1959.

Hine, "Physical Organic Chemistry," 2d ed., McGraw-Hill Book Company, New York, 1962.

Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1953.

Morrison and Boyd, "Organic Chemistry," 2d ed., Allyn and Bacon, Inc., Boston, 1966.

Noller, "The Chemistry of Carbon Compounds," 3d ed., W. B. Saunders Company, Philadelphia, 1965.

Roberts and Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, Inc., New York, 1964.

Royals, "Advanced Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N.J., 1954.

Wheland, "Advanced Organic Chemistry," 3d ed., John Wiley & Sons, Inc., New York, 1960.

Wiberg, "Physical Organic Chemistry," John Wiley & Sons, Inc., New York, 1964.

Other Books. In this section we mention several books which do not fit conveniently into the previous categories. All have to do with laboratory synthesis.

1. *Organic Syntheses,* published by John Wiley & Sons, Inc., New York, is a collection of procedures for the preparation of specific compounds. The

thin annual volumes have appeared each year since 1921. The procedures for each ten (or nine) year period are collected in cumulative volumes, in this manner:

Annual volumes	*Collective volumes*
1–9	I
10–19	II
20–29	III
30–39	IV

The advantage of the procedures in *Organic Syntheses,* compared to those found in original journals, is that these procedures are *tested.* Each preparation is carried out first by its author and then by a member of the *Organic Syntheses* editorial board, and only if the yield is essentially duplicated is the procedure published. While it is possible to repeat most procedures given in journals, this is not always the case. All *Organic Syntheses* preparations are noted in Beilstein and in *CA*. In order to locate a given reaction in *Organic Syntheses,* the reader may use the OS references given in the present volume (through OS **46**); the indexes in *Organic Syntheses* itself; or Sugasawa and Nakai, "Reaction Index of Organic Syntheses," John Wiley & Sons, Inc., New York, 1967 (through OS **45**).

2. Theilheimer, "Synthetic Methods of Organic Chemistry," S. Karger Verlag, Basel, is an annual compilation, beginning in 1946, of new methods for the synthesis of organic compounds, arranged according to a system based on bond closings and bond breakings. Equations, brief procedures, yields, and literature references are given. Volume 21 was issued in 1967. Volumes 3 and 4 are available only in German, but all the rest are in English. There is an index to each volume. Cumulative indexes appear in every fifth volume. Beginning with Vol. 8, each volume includes a short summary of trends in synthetic organic chemistry.

3. "Newer Methods of Preparative Organic Chemistry" is a collection of review articles on synthetic methods, reprinted from *Angewandte Chemie.* Volume 1 appeared in English translation in 1948 (published by Interscience Publishers, Inc., New York). The English translations of Vols. 2 and 3, edited by Foerst and published by Academic Press Inc., New York, appeared in 1963 and 1964. Further volumes are in prospect.

4. "Synthetic Organic Chemistry," by Wagner and Zook, John Wiley & Sons, Inc., New York, 1953, discusses, in separate numbered sections, the scope and limitations of 576 reactions, divided into 39 chapters, each of which covers the preparation of a specific type of compound, e.g., olefins, cyanides, lactones, etc. An important and useful feature of the book is the large number of tables which list the best method of preparation, the yield, and physical constants, for thousands of compounds containing no more than two functional groups. References are given for all data.

5. "Reagents for Organic Synthesis," by Fieser and Fieser, John Wiley & Sons, Inc., New York, 1967, is a 1457-page volume which discusses, in separate

sections, some 1120 reagents and catalysts. It tells how each reagent is used in organic synthesis (with references), and for each, tells which companies sell it, or how to prepare it, or both. The listing is alphabetical.

LITERATURE SEARCHING

Information about a Specific Compound. Most organic chemists find it necessary, occasionally or frequently, to search the literature for information concerning specific compounds. They may need to know if a compound has ever been prepared and, if so, how, and/or they may be seeking a melting point, an infrared spectrum, or some other property. The directions for this particular type of literature search are so much more specific than for other searches that we discuss them first. If one desires all the information that has ever been published on any compound, he begins by consulting the formula index to the second supplement of Beilstein (p. 943). Here he will quickly find out whether the compound is mentioned in the literature through 1929. If it is there, he turns to the pages indicated, where all methods used to prepare the compound are given, as well as all physical properties, with references. If the compound is in a volume of Beilstein of which the third supplement has been published, he then looks for it there, by the method described on page 943. If the compound is not listed in the cumulative formula index (and is thus absent from the literature through 1929), the next step is to ascertain whether it is in the third supplement, which may be done as described on page 943. At this point the investigator will know (1) all information published through 1949; (2) that the compound is not mentioned in the literature through 1949; (3) all information published through 1929; or (4) that the compound is not mentioned in the literature through 1929.[24] In some cases, scrutiny of Beilstein will be sufficient, perhaps if only a boiling point or a refractive index is required. In other cases, especially where specific laboratory directions are needed, the investigator will have to turn to the original papers.

To carry the search past 1929 (or 1949), the chemist next turns to the collective formula indexes of *Chemical Abstracts:* 1920–1946 (if this period was not covered by Beilstein); 1947–1956; 1957–1961; such later collective indexes as have appeared; and the semiannual indexes thereafter. The use of these indexes is somewhat different from that of the Beilstein index. Instead of only three (or fewer) pages, the user is likely to be referred to many pages. Each page contains an abstract in which the given compound is mentioned. In some cases (the index entry is marked by an asterisk), the compound is not mentioned in the abstract, though it is in the original paper or patent. Incidentally, all entries in the *CA* indexes which refer to patents are prefixed by the letter P. The number of page references may be very large, and the numerous subheadings given often help the user to narrow his search to the more promising entries. Nevertheless, he will undoubtedly turn to many abstracts which do not prove to be helpful. In many cases, the information in the abstracts will be sufficient. If not, the original references must be consulted.

---

[24] Categories (1) and (2) apply to compounds which would naturally belong to those volumes of the third supplement which are already published, whether or not they are mentioned in the third supplement. Categories (3) and (4) apply to compounds which belong to the later volumes of Beilstein.

By the procedure outlined above, all information regarding a specific compound which has been published up to about a year before the search may be found by a procedure which is always straightforward and which in many cases is rapid (if the compound has been reported only a few times). Equally important, if the compound has not been reported, the investigator will know that, too. It should be pointed out that, for common compounds, such as benzene, ether, acetone, etc., trivial mentions in the literature are not indexed (so that they will not be found by this procedure), only significant ones. Thus, if acetone is converted to another compound, an index entry will be found, but not if it is used as a solvent or an eluent in a common procedure.

There are several methods for learning whether a compound is mentioned in the literature after the period covered by the latest semiannual formula index of *CA*. One may consult *Chemical Titles* and the KWIC index (p. 940) at the end of each issue of *CA*. In these cases, of course, it is necessary to know what name might be used for the compound. The name is not necessary for *Index Chemicus* (p. 941); one consults the formula indexes, which appear three times a year. However, these methods are far from complete. *Index Chemicus* lists only *new* compounds, those that would not have been found in the earlier search. As for *Chemical Titles*, the compound can be found only if it is mentioned in the title. The KWIC indexes in *CA* are more complete, being based on internal subject matter as well as title, but they are by no means exhaustive. Furthermore, all three of these publications lag at some distance behind the original journals, though *Chemical Titles* is very close. There is no method for the *complete* location of all references to a compound after the period covered by the latest semiannual formula index of *CA*.

The complete procedure described above may not be necessary in all cases. Often all the information one needs about a compound will be found in one of the handbooks (p. 944), in the "Dictionary of Organic Compounds" (p. 944), or in one of the other compendia listed in this chapter, most of which give references to the original literature.

Other Searches.[25] There is no definite procedure for making other literature searches. If a chemist wishes to know all that is known about the mechanism of the reaction between aldehydes and HCN; or which compounds of the general formula Ar_3CR have been prepared; or which are the best catalysts for Friedel-Crafts acylation of naphthalene derivatives with anhydrides; or where the group $C(NH_2){=}NH$ absorbs in the infrared, he is dependent on his ingenuity and his knowledge of the literature. If a specific piece of information is needed, he may be able to find it in one of the compendia mentioned previously and in Chapter 6. If the topic is more general, it is often the best procedure to begin by consulting one or more monographs, treatises, or textbooks, which will give general background information and often provide references to review articles and to original papers. For example, Olah's treatise (p. 948) should certainly be consulted on the Friedel-Crafts topic mentioned above. In many cases this is sufficient, but when a complete search is required, it is necessary to consult the *CA* subject indexes, where the ingenuity of the investigator is most required, for now he must decide which words to look under. If he is interested in the mechanism of the reaction between aldehydes and HCN, he might look under "aldehydes", or "hydrogen cyanide"; or even under "acetaldehyde" or "benzaldehyde," etc., but then the search is likely to prove long. A better choice in this case would be "cyanohydrin," since these are the normal products, and references there would be fewer. He would probably waste his time if he looked under "mechanism." In any case, many of the abstracts would prove not to be helpful. Literature searching of this kind is necessarily a wasteful process. Of course, the searcher would not consult the *CA* annual indexes, but only the collective indexes as far as they go, and the semiannual indexes thereafter. If it is necessary to search before 1907 (and even before 1920, since *CA* was not very complete from 1907 to about 1920), recourse may be made to *Chemisches Zentralblatt* (p. 941) and to the abstracts in the *Journal of the Chemical Society* (p. 941).

---

[25] This discussion is necessarily short. For much more extensive discussions, see Mellon, Ref. 1, pp. 218–229; Crane, Patterson, and Marr, Ref. 1, pp. 297–325.

How to Locate Journal Articles. Having obtained a reference from Beilstein, *CA*, a treatise, or some other source, one often needs to consult the original journal (the location of patents is discussed on p. 936). The first step is to ascertain the full name of the journal, since it is the abbreviation which is generally given. Of course, everyone should be familiar with the abbreviations of the very important journals, such as *J. Chem. Soc., Chem. Ber.,* etc., but references are often found to journals whose titles are not at all familiar (e.g., *Kgl. Skogs. Lantbruksakad. Tidskr.* or *Nauchn. Tr. Mosk. Lesotekhn. Inst.*). In such cases, one consults the *Chemical Abstracts* "List of Periodicals," which is issued along with the *CA* indexes and which contains the names of all journals covered by *CA,* with the abbreviations in bold print. The journals are listed in alphabetical order of the *abbreviations,* not of the titles. The latest complete list appeared in 1961. Supplements have been issued almost each year since then to cover new journals and those which change titles. It should be pointed out that, while many publications use the *CA* abbreviations, not all do. The student will find that usages vary from country to country, and even from journal to journal within a country. Furthermore, the *CA* abbreviations change from time to time.

Once the complete title is known, the journal can easily be obtained, if it is in the library customarily used by the chemist. If not, one must use another library, and the next step is to find out which libraries carry the journal. The *CA* "List of Periodicals" (complete versions, not supplements) answers this question too, since it carries a list of some 300 libraries in the United States and foreign countries, and *for each journal it tells which of* *these libraries carries it.*[26] It may be possible to visit the closest library personally. If not, many of these libraries maintain one or more of the following services: lending, microfilms, photocopying; and a copy of the article may be obtained in one of these ways, with photocopying being most common. Which of these services is provided is indicated for each library on the *CA* list. Photocopies of original Russian articles may be obtained from Chemical Abstracts Service, The Ohio State University, Columbus, Ohio, 43210.

---

[26] The list indicates only the journals currently received by the library, but most libraries have substantial back files.

APPENDIX C

Classification of Reactions by Type of Compound Synthesized

Acetals and Ketals

0-16 Reaction between alkoxides and *gem*-dihalides (Williamson)
0-21 Transetherification
0-75 Reduction of ortho esters
0-83 Reaction between Grignard reagents and ortho esters
5-5 Addition of alcohols or phenols to triple bonds
6-6 Addition of alcohols to aldehydes or ketones
6-51 Addition of aldehydes to olefins (Prins)
6-57 Trimerization and polymerization of aldehydes

Acetylenes (*see* Alkynes)

Acetylenic Ethers

7-14 Reaction between vinylidine dihalides and amide ion

Acids (*see* Carboxylic Acids, Sulfonic Acids)

Acylals

5-6 Addition of acids to alkynes
6-55 Acylation of aldehydes or ketones
9-15 Bisdecarboxylation of malonic acids

Acyl Halides

0-62 Halide exchange
0-70 Reaction between acids and inorganic acid halides
0-71 Reaction between esters or anhydrides and inorganic acid halides
0-72 Reaction between hydrazides, chlorine, and HCl
4-3 Halogenation of aldehydes
5-1 Addition of hydrogen halides to ketenes
5-16 Free-radical addition of acyl halides to olefins
5-27 Reaction between olefins, carbon monoxide, and $PdCl_2$

Acyloins (*see* Hydroxy Aldehydes and Ketones)

Acyloxy Amides

6-69 Reaction between isonitriles, acids, and aldehydes or ketones (Passerini)

Alcohols (*see also* Diols, Hydroxy Esters, etc.)

0-1 Hydrolysis of alkyl halides
0-4 Hydrolysis of inorganic esters

0-5	Diazotization of primary aliphatic amines
0-7	Hydrolysis of vinyl ethers, acetals, or ortho esters
0-11	Hydrolysis of esters
0-13	Decarbonylation of acids
0-21	Transetherification
0-26	Transesterification
0-30	Reaction between acids and esters
0-54	Ammonolysis of esters
0-65	Cleavage of ethers with concentrated acids
0-76	Reduction of epoxides
0-83	Cleavage of acetals or ortho esters with Grignard reagents
0-84	Reaction between Grignard reagents and epoxides
1-12	Alkylation of aromatic rings with ethylene oxide
1-24	Hydroxyalkylation of aromatic rings
2-15	Reaction between Grignard reagents and oxygen
4-4	Hydroxylation at an aliphatic carbon
5-2	Hydration of olefins
5-16	Free-radical addition of alcohols to olefins
6-27	Reduction of aldehydes or ketones
6-31	Addition of Grignard reagents to aldehydes or ketones
6-33	Addition of Grignard reagents to esters or acyl halides
6-51	Reaction between aldehydes, olefins, and sodium
7-2	Alkaline cleavage of ethers
8-1	Rearrangement of alcohols or olefins (Wagner-Meerwein)
8-3	Expansion and contraction of rings (Demyanov)
8-21	Cleavage of hydroperoxides
8-23	Rearrangement of ethers upon treatment with alkyllithiums (Wittig)
9-10	Reduction of ozonides
9-30	Coupling of primary alcohols (Guerbet)
9-35	Reduction of carboxylic acids
9-39	Reduction of esters
9-40	Reduction of anhydrides
9-41	Reduction of acyl halides
9-50	Reduction of hydroperoxides
9-54	Reduction of peroxides
9-62	Reaction between aldehydes and base (Cannizzaro)

Aldehydes (*see also* Dicarbonyl Compounds, Unsaturated Carbonyl Compounds, etc.)

0-2	Hydrolysis of *gem*-dihalides
0-7	Hydrolysis of vinyl ethers or acetals
0-26	Alcoholysis of enol esters
0-30	Reaction between enol esters and carboxylic acids
0-78	Reduction of acyl halides (Rosenmund)
0-79	Reduction of acids or esters
0-80	Reduction of amides
0-90	Reaction between formates or formamides and organometallic compounds

0-98	Reaction between formic acid, another acid, and thorium oxide
1-16	Formylation of aromatic rings with carbon monoxide and HCl (Gatterman-Koch)
1-17	Formylation of aromatic rings with HCN and HCl (Gatterman)
1-18	Formylation of aromatic rings with formamides and $POCl_3$ (Vilsmeier)
1-19	Formylation of aromatic rings with formyl fluoride
1-20	Formylation of aromatic rings with dichloromethyl methyl ether
1-21	Formylation of aromatic rings with chloroform (Reimer-Tiemann)
1-42	Reaction between arylcarbinols and diazonium salts (Stiles-Sisti)
2-26	Decarboxylation of α-keto or glycidic acids
5-3	Hydration of acetylene
5-13	Hydrolysis of unsaturated boranes
5-15	Addition of aldehydes to activated olefins (Michael)
5-19	Hydroformylation of olefins (oxo process)
6-2	Hydrolysis of imines, oximes, hydrazones, or other C=N compounds
6-4	Hydrolysis of primary nitro compounds (Nef)
6-30	Reduction of nitriles
7-1	Dehydration of 1,2-diols
7-2	Pyrolysis of vinyl ethers
7-26	Fragmentation of γ-amino or γ-hydroxy halides
7-28	Fragmentation of 1,3-diols or γ-amino alcohols
7-31	Fragmentation of certain ketoximes
7-34	Alkaline hydrolysis of nitrates
7-35	Pyrolysis of β-hydroxy olefins
7-36	Pyrolysis of allyl ethers
8-9	Homologization of aldehydes
8-15	Reaction between α-hydroxy or α-halo amides and NaOBr (Hofmann)
8-21	Cleavage of hydroperoxides
8-32	Photolysis of nitrites, followed by hydrolysis (Barton)
9-3	Oxidation of primary alcohols
9-8	Oxidative cleavage of glycols or related compounds
9-10	Ozonolysis of olefins
9-11	Oxidative cleavage of certain olefins
9-16	Oxidation of activated methyl groups
9-17	Oxidation of arylmethanes (Étard)
9-19	Oxidation of primary halides or esters of primary alcohols
9-21	Oxidation of olefins with noble-metal salts

Alkanes (*see also* Cycloalkanes)

0-73	Reduction of alkyl halides
0-74	Hydrogenolysis of alcohols
0-75	Reduction of ethers
0-77	Reduction of primary amines or quaternary ammonium or phosphonium salts
0-81	Coupling of alkyl halides (Wurtz)
0-82	Reaction between Grignard reagents and alkyl sulfates or sulfonates
0-83	Reaction between Grignard reagents and ethers
1-43	Reduction of aromatic ethers

2-11 Insertion of carbenes
2-14 Reaction between organometallic compounds and acids
2-26 Decarboxylation of carboxylic acids
2-27 Cleavage of tertiary alkoxides
2-31 Cleavage of nonenolizable ketones
2-32 Cleavage of ketones with amide ion (Haller-Bauer)
4-22 Coupling of organometallic compounds
4-23 Coupling of boranes
4-24 Desulfurization of sulfur compounds
4-25 Decarboxylative dimerization (Kolbe)
4-27 Decarbonylation of aldehydes
5-11 Reduction of olefins and alkynes
5-12 Reduction of aromatic rings
5-14 Addition of alkanes to olefins
5-17 Reductive coupling of olefins
9-6 Oxidation of hydrazines
9-11 Cleavage of olefins with hydrazinium ion
9-34 Reduction of aldehydes or ketones (Wolff-Kishner; Clemmensen)
9-46 Reduction of cyano to methyl groups

Alkenes (*see also* Unsaturated Acids, Unsaturated Alcohols, etc.)

0-7 Acid cleavage of *tert*-butyl ethers
0-66 Reduction of α-keto epoxides
2-2 Migration of double and triple bonds
2-26 Decarboxylation of unsaturated acids
4-16 Arylation of olefins (Meerwein)
4-25 Additive dimerization of olefins and carboxylic acids
5-11 Selective reduction of alkynes or allenes
5-12 Reduction of aromatic rings
5-14 Dimerization of olefins
5-34 Addition of olefins to dienes (Diels-Alder)
5-35 Dimerization of dienes
5-36 Tetramerization of alkynes
5-37 Addition of carbenes to aromatic rings
6-27 Reduction of α,β-unsaturated ketones with $LiAlH_4$
6-42 Reaction between anhydrides and aldehydes
6-45 Reaction between phosphorus ylides and aldehydes or ketones (Wittig)
7-1 Dehydration of alcohols
7-2 Alkaline cleavage of ethers
7-3 Pyrolysis of carboxylic esters
7-4 Pyrolysis of xanthates (Chugaev)
7-5 Cleavage of inorganic esters and sulfonates
7-6 Cleavage of quaternary ammonium hydroxides (Hofmann)
7-7 Cleavage of quaternary ammonium salts
7-8 Cleavage of amine oxides (Cope)
7-10 Cleavage of aliphatic diazonium salts
7-11 Decomposition of tosylhydrazones (Bamford-Stevens)
7-12 Cleavage of sulfonium compounds

7-13 Cleavage of sulfones and sulfoxides
7-14 Dehydrohalogenation of alkyl halides
7-16 Elimination of boranes
7-17 Cleavage of Michael adducts
7-18 Pyrolysis of alkali organometallic compounds
7-19 Cleavage of cyclic thionocarbonates
7-20 Deoxidation of epoxides
7-21 Desulfurization of episulfides; elimination from α-halo sulfones
7-22 Dehalogenation of *vic*-dihalides
7-24 Elimination of a halo and a hetero group (Boord)
7-25 Fragmentation of γ-branched alcohols or halides
7-26 Fragmentation of γ-amino or γ-hydroxy halides
7-28 Fragmentation of 1,3-diols or γ-amino alcohols
7-35 Pyrolysis of β-hydroxy olefins
7-36 Pyrolysis of allyl ethers
8-1 Rearrangement of alcohols and olefins (Wagner-Meerwein)
8-3 Expansion and contraction of rings (Demyanov)
8-26 Rearrangement of 1,5-dienes and 1,3,5-trienes (Cope); cleavage of cyclobutanes; rearrangement of cyclobutenes
9-15 Bisdecarboxylation of succinic acids
9-29 Oxidative coupling of halides
9-34 Reduction of α-hydroxy ketones

Alkyl Halides (*see also* Dihalides, Halohydrins, etc.)

0-62 Halide exchange (Finkelstein)
0-63 Reaction between inorganic esters and halide ions
0-64 Reaction between alcohols and hydrogen halides or inorganic acid halides
0-65 Cleavage of ethers with HI or HBr
0-68 Cleavage of tertiary amines (von Braun)
0-69 Cleavage of amines with hydrohalic acids
0-73 Reduction of dihalides
1-12 Reaction between aromatic rings and carbon tetrachloride
1-25 Haloalkylation of aromatic rings
2-19 Halogenation of Grignard reagents
2-25 Exchange between halides and organometallic compounds
4-1 Free-radical halogenation
4-2 Allylic halogenation
4-26 Decarboxylative halogenation (Hunsdiecker)
4-28 Decomposition of tertiary hypochlorites
5-1 Addition of hydrogen halides to olefins
5-16 Free-radical addition of alkyl halides to olefins
5-22 Addition of halogens to olefins or alkynes
5-26 Addition of alkyl or aryl halides to olefins

Alkynes (*see also* Acetylenic Ethers)

0-87 Alkylation at an acetylenic carbon
2-2 Triple-bond migration

2-26 Decarboxylation of acetylenic acids
2-32 Cleavage of α,β-acetylenic acid derivatives with amide ion
3-14 Reaction between aryl iodides and copper acetylides
4-14 Coupling of alkynes (Glaser)
7-6 Pyrolysis of bisquaternary ammonium hydroxides
7-11 Reaction between bistosylhydrazones and mercuric oxide
7-14 Dehydrohalogenation of dihalides or vinyl halides
7-22 Dehalogenation of tetrahalides
7-27 Fragmentation of β-halo acrylic acid salts or α-chloroacroleins
8-10 Rearrangement of vinyl halides (Fritsch-Buttenberg-Wiechell)

Allenic Aldehydes

8-25 Rearrangement of propargyl vinyl ethers

Amidals (*see* Bisamides)

Amides (*see also* Bisamides)

0-12 Cleavage of an alkyl group from N-*tert*-butyl amides
0-50 Reaction between secondary amines and chloroform
0-51 Amination of acyl halides
0-52 Amination of anhydrides
0-53 Amination of acids
0-54 Amination of esters
0-55 Amination of amides
0-56 Amination of other acid derivatives
0-57 N-Alkylation of amides
1-15 Amidation of aromatic rings with isocyanates
1-36 Rearrangement of N-halo-N-acyl aromatic amines (Orton)
2-32 Cleavage of ketones with amide ion (Haller-Bauer)
5-9 Addition of amides to olefins; addition of amines to ketenes
5-16 Free-radical addition of amides to olefins
5-18 Hydrocarboxylation of olefins in the presence of amines
6-5 Partial hydrolysis of nitriles
6-16 Reductive alkylation of amines (Leuckart)
6-36 Addition of Grignard reagents to isocyanates
6-54 Addition of alcohols or other carbonium-ion sources to nitriles (Ritter)
6-67 Addition of water to isonitriles
8-7 Rearrangement of α-halo ketones in the presence of amines (Favorskii)
8-8 Rearrangement of diazo ketones in the presence of amines (Arndt-Eistert)
8-15 Reaction between amides, lead tetraacetate, and acetic acid
8-18 Reaction between ketones and hydrazoic acid (Schmidt)
8-19 Rearrangement of oximes (Beckmann)
8-31 Rearrangement of aryl imidates (Chapman)
9-64 Oxidation of aryl ketones with ammonium polysulfide (Willgerodt)

Amidines

5-9 Addition of amines to ketenimines
6-19 Addition of ammonia or amines to nitriles

Aminals

6-15	Addition of amines to aldehydes or ketones

Amine Oxides

9-25	Oxidation of tertiary amines

Amines (*see also* Cyanoamines, Amino Acids, etc.)

0-12	Hydrolysis of amides
0-44	Alkylation of ammonia or amines
0-45	Reaction between alkyl halides and hexamethylenetetramine
0-46	Indirectly, from alcohols
0-47	Transamination
0-48	Alkylation of amines with diazo compounds
0-54	Cleavage of esters with amines
0-57	Hydrolysis of phthalimides (Gabriel)
0-69	Cleavage of aromatic amines
0-77	Reduction of quaternary ammonium salts or aziridines
0-83	Cleavage of amine ethers with Grignard reagents
1-6	Direct amination of aromatic rings
1-26	Aminoalkylation of aromatic rings
1-33	Rearrangement of N-nitroamines
1-34	Rearrangement of N-nitrosoamines (Fischer-Hepp)
1-35	Rearrangement of triazenes
1-37	Rearrangement of aryl alkyl ammonium salts (Hoffmann-Martius)
3-6	Arylation of ammonia or amines
3-7	Reaction between naphthols, bisulfite ion, and ammonia or amines (Bucherer)
3-18	Amination of heterocyclic nitrogen compounds (Chichibabin)
3-19	Direct amination of activated aromatic rings
3-27	Rearrangement of benzyl quaternary ammonium salts (Sommelet-Hauser)
3-28	Rearrangement of aryl hydroxylamines
5-9	Addition of ammonia or amines to olefins
5-16	Free-radical addition of amines to olefins
6-3	Hydrolysis of isocyanates or isothiocyanates
6-14	Addition of ammonia to aldehydes
6-16	Reductive alkylation of ammonia or amines
6-17	Reaction between aldehydes, ammonia or amines, and an active hydrogen compound (Mannich)
6-28	Reduction of imines, hydrazones, or other compounds containing the C=N bond
6-29	Reduction of nitriles
6-33	Addition of Grignard reagents to formamides
6-35	Addition of Grignard reagents to imines
6-68	Reduction of isonitriles
7-6	Cleavage of quaternary ammonium hydroxides (Hofmann)
7-7	Cleavage of quaternary ammonium salts

7-31 Fragmentation of certain ketoximes
8-15 Reaction between amides and NaOBr (Hofmann)
8-16 Rearrangement of acyl azides in the presence of water (Curtius)
8-17 Rearrangement of hydroxamic acids (Lossen)
8-18 Addition of hydrazoic acid to carboxylic acids (Schmidt)
8-22 Rearrangement of quaternary ammonium salts (Stevens)
8-24 Rearrangement of benzidines
9-10 Reaction between ozonides, ammonia, and hydrogen
9-36 Reduction of amides
9-42 Reduction of nitro compounds
9-44 Reduction of nitroso compounds or hydroxylamines
9-45 Reduction of oximes
9-46 Reduction of isocyanates, isothiocyanates, or azides
9-48 Reduction of amine oxides
9-52 Reduction of azo, azoxy, or hydrazo compounds
9-57 Bimolecular coupling of imines

Amino Acids and Esters

0-12 Hydrolysis of lactams
0-44 Amination of halo acids
0-86 Alkylation of N-acetylaminomalonic ester (Sorensen)
2-7 Nitrosation at a carbon bearing an active hydrogen and reduction of the resulting oxime or nitroso compound
6-5 Hydrolysis of cyanohydrins
6-17 Reaction between aldehydes, ammonia, and carboxylic acids
6-42 Reduction of azlactones
8-15 Reaction between imides and NaOBr (Hofmann)
8-28 Rearrangement of hydroxy amides
9-53 Reduction of azlactones

Amino Carbonyl Compounds

0-47 Transamination of Mannich bases
6-17 Reaction between aldehydes, ammonia, and aldehydes, ketones, or esters (Mannich)
8-14 Rearrangement of ketoxime tosylates (Neber)
8-22 Rearrangement of quaternary ammonium salts (Stevens)

Amino Ethers

0-22 Alcoholysis of aziridines

Amino Mercaptans

0-49 Amination of episulfides
1-9 Sulfurization of aromatic amines (Herz)

Anhydrides

0-29 Reaction of acyl halides with acid salts
0-30 Dehydration of acids
0-33 Reaction of acid derivatives with inorganic acids

4-10	Acyloxylation of aldehydes
5-6	Addition of acids to ketenes
8-20	Reaction between α-diketones and peroxy compounds (Baeyer-Villiger)
9-11	Oxidation of aromatic rings
9-54	Reduction of acyl peroxides

Arenes

0-74	Hydrogenolysis of benzyl alcohols
0-75	Reduction of benzyl ethers
1-12	Alkylation of aromatic rings (Friedel-Crafts)
1-13	Arylation of aromatic rings (Scholl)
1-24	Diarylation of ketones; ring closure of aryl-substituted carbonyl compounds (Bischler-Napieralski, Skraup, Pechmann)
1-38	Cleavage or rearrangement of alkyl arenes
1-39	Decarbonylation of aromatic aldehydes
1-40	Decarboxylation of aromatic acids
1-43	Reduction of aromatic ethers
1-44	Desulfonation of aromatic sulfonic acids
1-45	Dehalogenation of aryl halides
1-47	Hydrolysis of organometallic compounds
2-26	Decarboxylation of α-aryl acids
2-27	Cleavage of tertiary alkoxides
3-9	Reduction of phenols, phenolic ethers, or phenolic esters
3-10	Reduction of aromatic nitro compounds
3-13	Coupling of organometallic compounds with aryl ethers
3-16	Coupling of aryl iodides (Ullmann)
3-17	Alkylation with organolithium compounds
3-25	Reduction of diazonium salts
4-15	Free-radical arylation by diazonium salts (Gomberg-Bachmann, Pschorr)
4-17	Free-radical arylation by peroxides
4-21	Dimerization of diazonium salts
4-22	Coupling of organometallic compounds
4-24	Reduction of sulfur compounds
5-17	Reductive coupling of olefins
5-36	Trimerization of alkynes
6-45	Reaction between ylides and pyrilium salts
8-26	Pyrolysis of phenyltrienes followed by aromatization
9-1	Aromatization of six-membered rings
9-2	Cyclodehydrogenation of aliphatic chains
9-6	Oxidation of hydrazines

Aryl Halides

1-11	Halogenation of aromatic compounds
1-36	Rearrangement of N-haloamines (Orton)
1-45	Migration of halogen

2-19	Reaction between aryl Grignard reagents and halogens
3-8	Aryl halide exchange
3-23	Reaction between diazonium salts and iodide ion
3-24	Heating of diazonium fluoborates (Schiemann)
4-18	Reaction between diazonium salts and CuCl or CuBr (Sandmeyer)
4-27	Decarbonylation of acyl halides

Azides

0-60	Alkylation or acylation of azide ion
2-34	Reaction between hydrazines and nitrous acid
5-25	Treatment of olefins with sodium azide, ferric chloride, ferrous sulfate, and hydrogen peroxide
5-32	Treatment of olefins with sodium azide, ferrous ion, and hydrogen peroxide
8-16	Reaction between hydrazides and nitrous acid
8-18	Reaction between alcohols or olefins and hydrazoic acid

Azines

6-21	Addition of hydrazine to aldehydes or ketones

Aziridines

0-44	Cyclization of haloamines
6-35	Reaction between Grignard reagents and oximes
6-64	Addition of divalent carbon to C=N bonds
9-45	Reduction of oximes

Azlactones

6-42	Condensation between aldehydes and N-acylglycines (Erlenmeyer)

Azo Compounds

1-4	Coupling of diazonium salts with aromatic rings
1-35	Rearrangement of aryl triazenes
1-42	Reaction between aromatic alcohols and diazonium salts (Stiles-Sisti)
1-47	Reaction between organometallic compounds and diazonium ions
2-6	Aliphatic diazonium coupling
4-21	Coupling of aryl diazonium salts
8-33	Rearrangement of azoxy compounds (Wallach)
9-6	Oxidation of hydrazines
9-32	Oxidation of amines
9-48	Reduction of azoxy compounds
9-60	Reduction of nitro compounds

Azoxy Compounds

9-26	Oxidation of azo compounds
9-59	Reduction of nitro or nitroso compounds; reaction between nitroso compounds and hydroxylamines

Benzoins (*see* Hydroxy Aldehydes and Ketones)

Bisamides

6-15	Addition of amides to aldehydes or ketones
6-58	Addition of nitriles to aldehydes
6-69	Reaction between isonitriles, acids, amines, and aldehydes or ketones (Passerini)

Bisulfite Addition Compounds (*see* Hydroxy Sulfonic Acids)

Boranes

2-21	Reaction between boron halides and Grignard reagents
5-13	Hydroboration of olefins or alkynes
7-16	Exchange reaction between boranes and olefins
8-12	Migration of boron

Bunte Salts

0-40	Reaction between alkyl halides and thiosulfate ion

Carbamates

0-51	Reaction between chloroformates and primary amines
0-61	Reaction between alkyl halides, ethanol, and thiocyanate ion
2-32	Cleavage of α,β-acetylenic esters with amide ion
5-9	Addition of carbamates to olefins
6-8	Addition of alcohols to isocyanates
6-70	Addition of alkyl hypochlorites to isonitriles
8-15	Reaction between amides, bromine, and alkoxides (Hofmann); reaction between amides, lead tetraacetate, and acetic acid
8-16	Rearrangement of acyl azides in the presence of alcohols (Curtius)

Carbodiimides

6-59	Addition of isocyanates to isocyanates

Carbonates

0-23	Alcoholysis of phosgene

Carboxylic Acids

0-3	Hydrolysis of 1,1,1-trihalides
0-7	Hydrolysis of ortho esters
0-9	Hydrolysis of acyl halides
0-10	Hydrolysis of anhydrides
0-11	Hydrolysis of esters
0-12	Hydrolysis of amides
0-24	Alcoholysis of anhydrides
0-52	Amination of anhydrides
0-54	Cleavage of esters with amines
0-70	Exchange between acids and acyl halides
0-86	Hydrolysis of malonic or acetoacetic esters
1-22	Carboxylation of aromatic rings with carbonyl halides

1-23 Carboxylation of aromatic rings with carbon dioxide (Kolbe-Schmitt)
1-40 Rearrangement of aromatic carboxylate ions
2-26 Decarboxylation of dicarboxylic acids
2-29 Basic cleavage of β-keto esters or β-diketones
2-30 The haloform reaction
2-31 Cleavage of nonenolizable ketones
3-26 Rearrangement of aromatic nitro compounds upon treatment with cyanide ion (von Richter)
4-6 Oxidation of aldehydes
5-2 Addition of water to ketenes
5-14 Addition of carboxylates to olefins
5-16 Free-radical addition of acids to olefins
5-18 Hydrocarboxylation of olefins
6-4 Hydrolysis of primary nitro compounds
6-5 Hydrolysis of nitriles
6-34 Addition of Grignard reagents to carbon dioxide
7-3 Pyrolysis of carboxylic esters
7-31 Fragmentation of certain ketoximes
8-7 Rearrangement of α-halo ketones (Favorskii)
8-8 Rearrangement of diazo ketones (Arndt-Eistert)
9-8 Oxidative cleavage of α-diketones and α-keto acids
9-9 Oxidative cleavage of ketones and secondary alcohols
9-10 Oxidation of ozonides; ozonolysis of alkynes
9-11 Oxidative cleavage of olefins
9-12 Oxidation of aromatic side chains
9-20 Oxidation of primary alcohols
9-62 Reaction between aldehydes and base (Cannizzaro)
9-64 Oxidation of aryl ketones by ammonium polysulfide (Willgerodt)

Carboxylic Esters (*see also* Dicarbonyl Compounds, Unsaturated Esters, etc.)

0-7 Hydrolysis of ortho esters
0-13 Decarbonylation of α-keto esters
0-23 Alcoholysis of acyl halides
0-24 Alcoholysis of anhydrides
0-25 Esterification of acids
0-26 Transesterification
0-27 Alkylation of acid salts
0-28 Alkylation of acids with diazo compounds
0-86 Alkylation of esters
0-89 Reaction between Grignard reagents and chloroformates
0-90 Reaction between Grignard reagents and carbonates
0-95 Reduction of β-carbalkoxyphosphoranes
1-30 Acyloxylation of aromatic rings
2-17 Esterification of enolates with acyl peroxides
2-29 Base cleavage of β-keto esters
3-4 Reaction between aryl halides and acid salts
3-14 Arylation of esters
3-15 Carbalkoxylation of aryl iodides

4-10	Free-radical acyloxylation
4-26	Reaction between silver salts and iodine (Simonini)
5-3	Hydration of acetylenic ethers
5-5	Addition of alcohols or phenols to ketenes
5-6	Addition of acids or acyl peroxides to olefins
5-15	Addition of esters to activated olefins (Michael)
5-16	Free-radical addition of esters to olefins
5-18	Hydrocarboxylation of olefins in the presence of alcohols
5-28	Addition of acid salts to olefins
6-10	Alcoholysis of nitriles
8-7	Rearrangement of α-halo ketones (Favorskii)
8-8	Rearrangement of diazo ketones in the presence of alcohols (Arndt-Eistert)
8-20	Reaction between ketones and peroxy compounds (Baeyer-Villiger)
9-3	Oxidation of acetals
9-14	Reaction between aromatic acids and lead tetraacetate
9-20	Oxidation of primary alcohols
9-38	Reduction of anhydrides
9-63	Reaction between aldehydes and aluminum ethoxide (Tishchenko)

Catena Compounds

9-58	Acyloin condensation or other methods

Cyano Acetals

0-88	Reaction between ortho esters and HCN

Cyanoamines

0-46	Amination of cyanohydrins
6-17	Reaction between aldehydes, ammonia, and nitriles (Mannich)
6-48	Addition of cyanide and ammonium ions to aldehydes or ketones (Strecker)
6-49	Addition of HCN to C=N bonds

N-Cyanoamines

0-68	Cleavage of tertiary amines with cyanogen bromide (von Braun)

Cyano Carbonyl Compounds

0-86	Alkylation of cyano carbonyl compounds
0-88	Reaction between β-dialkylaminoethyl aryl ketones and cyanide ion; reaction between lactones and cyanide ion
0-91	Acylation of nitriles by acyl halides
0-94	Acylation of nitriles by esters
0-96	Reaction between acyl halides and CuCN
2-10	Cyanoethylation of enamines
3-14	Arylation of cyano carbonyl compounds
5-15	Addition to olefins (Michael)
6-41	Addition of cyano carbonyl compounds to aldehydes or ketones (Knoevenagel)

6-46 Condensation of nitriles (Thorpe)
7-17 Reversal of the Michael reaction

Cyanohydrins (*see* Hydroxy Nitriles)

Cycloalkanes and Alkenes

0-81 Internal coupling (Wurtz)
0-85 Reaction between epoxides and phosphorus ylides
0-86 Internal malonic ester synthesis
2-11 Intramolecular insertion of carbenes
4-14 Coupling of terminal diynes (cycloalkynes)
5-6 Cyclization of olefinic acids
5-12 Reduction of aromatic rings
5-14 Cyclization of dienes
5-34 Addition of olefins to dienes (Diels-Alder)
5-35 Dimerization of olefins
5-36 Tetramerization of alkynes
5-37 Addition of carbenes or carbenoids to olefins or alkynes
8-3 Expansion and contraction of rings (Demyanov)
8-26 Rearrangement of 1,5-dienes or 1,3,5-trienes; ring expansion of vinylcycloalkanes

Dialdehydes (*see* Dicarbonyl Compounds)

Diazo Compounds

0-97 Reaction between acyl halides and diazomethane
2-33 Diazotization of α-amino esters and similar compounds
7-37 Elimination from N-nitroso-N-alkyl compounds
9-6 Oxidation of hydrazones

Diazonium Salts

1-5 Direct diazotization of aromatic rings
2-33 Diazotization of primary amines

1,2-Dicarbonyl Compounds

0-52 Reaction between α-amino acids and trifluoracetic anhydride
0-93 Condensation between esters and ethyl oxalate
3-15 Carboxalkylation of aryl iodides
6-2 Treatment of acyl azides successively with Ph_3P, water, and nitrous acid
6-42 Hydrolysis of azlactones
9-10 Ozonization of alkynes or aromatic rings
9-16 Oxidation of ketones with selenium dioxide
9-21 Oxidation of olefins

1,3-Dicarbonyl Compounds

0-86 Alkylation at a carbon bearing an active hydrogen
0-91 Acylation at a carbon bearing an active hydrogen
0-92 Acylation of ketones by anhydrides

0-93	Acylation of esters by esters (Claisen; Dieckmann)
0-94	Acylation of ketones by esters
2-9	Acylation of acetals or ketals followed by hydrolysis
2-10	Acylation of enamines followed by hydrolysis (Stork)
2-17	Esterification of enolates with acyl peroxides
3-14	Arylation at a carbon bearing an active hydrogen
5-15	Addition of active-hydrogen compounds to olefins (Michael)
5-16	Free-radical addition of 1,3-dicarbonyl compounds to olefins
6-32	Reaction between nitriles, zinc, and α-halo esters (Reformatsky)
6-41	Addition of 1,3-dicarbonyl compounds to aldehydes or ketones (Knoevenagel)
7-17	Cleavage of Michael adducts
9-29	Dimerization of β-keto esters or similar compounds

1,4-Dicarbonyl Compounds

0-7	Cleavage of furans
1-14	Acylation of aromatic rings by succinic anhydride
5-15	Addition of active-hydrogen compounds to olefins (Michael)
5-33	Reaction between ketene and diazo ketones
5-38	Reaction between alkynes, alkyl halides, and alcohols

Dicarboxylic Acids (*see* Dicarbonyl Compounds, Carboxylic Acids)

Dicyano Compounds

0-86	Alkylation of malononitriles
3-14	Arylation of malononitriles
5-15	Addition of nitriles to unsaturated nitriles (Michael)
6-41	Addition of malononitriles to aldehydes or ketones (Knoevenagel)
7-17	Cleavage of Michael adducts
9-11	Oxidation of *ortho*-diamines

Diesters (*see* Dicarbonyl Compounds)

Dihalides and Polyhalides

0-73	Reduction of trihalides
2-26	Decarboxylation of trihalo acids
2-30	The haloform reaction
4-1	Free-radical halogenation
5-1	Addition of hydrogen halides to alkynes
5-22	Addition of halogens to olefins or alkynes
5-26	Free-radical addition of polyhalides to olefins
6-26	Addition of PCl_5 or SF_4 to aldehydes or ketones

Diketones (*see* Dicarbonyl Compounds)

Dinitro Compounds

0-59	Reaction between salts of nitro compounds and silver nitrate
4-12	Nitration of paraffins
5-32	Addition of N_2O_4 to olefins
9-29	Dimerization of α-nitro compounds

gem-Diols (Hydrates)

6-1 Hydration of aldehydes

1,2-Diols

0-8 Hydrolysis of epoxides
5-28 Hydroxylation of olefins
9-57 Bimolecular reduction of aldehydes or ketones

1,3-Diols

6-44 Condensation between formaldehyde and aldehydes or ketones (Tollens)
6-51 Addition of aldehydes to olefins (Prins)

Disulfides

0-39 Reaction between alkyl halides and disulfide ion
3-5 Reaction between aryl halides and disulfide ion
9-31 Oxidation of mercaptans
9-47 Reduction of sulfonyl halides

Dithiocarbamates

6-20 Addition of amines to carbon disulfide

Dithiols

6-12 Addition of H_2S to carbonyl compounds or imines

Enamines

5-9 Addition of amines to triple-bond compounds
6-15 Addition of amines to aldehydes or ketones
6-17 Reaction between formic acid, secondary amines, and active-hydrogen compounds (Mannich)
9-1 Dehydrogenation of tertiary amines

Enolate Ions

2-3 Treatment of aldehydes or ketones with base
2-13 Treatment of active-hydrogen compounds with base

Enol Ethers and Esters

0-19 O-Alkylation of carbonyl compounds with diazo alkanes
0-23 Reaction between acyl halides and active-hydrogen compounds
5-5 Addition of alcohols or phenols to alkynes; addition of aldehydes or ketones to ketene
5-6 Addition of acids to alkynes
6-6 Addition of alcohols to aldehydes or ketones
6-42 Condensation between phthalic anhydride and other anhydrides
7-2 Cleavage of acetals
7-24 Elimination from β-halo acetals

Enol Thioethers

5-7 Addition of mercaptans to alkynes

Enynes

5-14 Dimerization of acetylenes

Epoxides

0-17 Cyclization of halohydrins
5-29 Epoxidation of olefins
6-43 Condensation between aldehydes and α-halo esters, ketones, or amides (Darzens)
6-62 Addition of diazomethane or ylides to aldehydes or ketones

Esters (*see* Carboxylic Esters, Inorganic Esters)

Ethers (*see also* Hydroxy Ethers, etc.)

0-11 Reaction between esters and alkoxide ion
0-16 Reaction between alkoxides or aroxides and alkyl halides (Williamson)
0-18 Reaction between alkoxides or aroxides and inorganic esters
0-19 Alkylation of alcohols or phenols with diazo compounds
0-20 Dehydration of alcohols
0-21 Transetherification
0-65 Cleavage of oxonium salts
0-75 Reduction of acetals or ketals
0-83 Reaction between Grignard reagents and acetals or ketals
2-16 Reaction between Grignard reagents and *tert*-butyl peresters
3-4 Reaction between aryl halides and alkoxides or aroxides
4-7 Cyclization of alcohols with lead tetraacetate
4-10 Free-radical alkyloxylation
5-5 Addition of alcohols or phenols to olefins
6-7 Reductive alkylation of alcohols
8-21 Dimerization of peroxides
9-37 Reduction of esters
9-54 Reduction of peroxides

Formazans

2-6 Coupling of diazonium salts with arylhydrazones

Fulvenes

6-41 Condensation between cyclopentadiene and aldehydes or ketones

Glycidic Esters

5-29 Epoxidation of α,β-unsaturated esters
6-43 Condensation between aldehydes or ketones and α-halo esters (Darzens)

Grignard Reagents (*see* Organometallic Compounds)

Halo Acids, Esters, Aldehydes, Ketones (*see* Halo Carbonyl Compounds)

Haloamines

5-25 Addition of N-haloamines to unsaturated compounds

N-Haloamines and Amides

2-36 Halogenation of amines or amides

Halo Carbonyl Compounds

0-67 Reaction of diazo ketones with hydrohalic acids
2-4 Halogenation of aldehydes or ketones
2-5 Halogenation of acids (Hell-Volhard-Zelinskii) and acid derivatives
5-22 Addition of halogens to ketenes
5-23 Addition of HOBr or HOCl to triple bonds
5-27 Addition of acyl halides to olefins
6-55 Reaction between acyl bromides and aldehydes or ketones

Halo Ethers and Acetals

2-4 Halogenation of acetals or ketals
5-23 Addition of hypochlorites to olefins or vinyl ethers
6-25 Addition of alcohols and hydrogen halides to aldehydes or ketones

Haloformic Esters

0-23 Alcoholysis of phosgene

Halohydrins

0-66 Cleavage of epoxides with hydrogen halides
5-23 Addition of hypohalous acids to olefins

Hemiacetals

6-6 Addition of alcohols to aldehydes or ketones

Hemiaminals

6-14 Reaction between aldehydes or ketones and ammonia
6-15 Reaction between aldehydes or ketones and amines

Hemihydrates

6-1 Hydration of aldehydes

Hemimercaptals

6-12 Addition of mercaptans to aldehydes or ketones

Heterocyclic Compounds (*see also* Epoxides, Aziridines, Lactams, Lactones, Anhydrides, Imides)

0-17 Cyclization of halohydrins (cyclic ethers)
0-20 Cyclization of glycols (cyclic ethers; furans)
0-21 Reaction of diols with acetals (cyclic acetals)
0-37 Reaction of dihalides with sulfide ion (cyclic sulfides)
0-44 Cyclization of haloamines (cyclic amines)
0-53 Dimerization of amino acids (diketopiperazines)
0-58 Reaction between ureas and malonic esters or between carbonates and malonamides (cyclic ureides)
1-9 Sulfurization of aromatic rings (cyclic sulfides)
1-14 Intramolecular acylation

1-15 Intramolecular amidation of aromatic rings
1-24 Cyclization of amides with $POCl_3$ (isoquinolines); reaction between aromatic amines, glycerol, sulfuric acid, and nitro compounds (quinolines); reaction between phenols and β-keto esters (coumarins)
2-6 Intramolecular aliphatic diazonium coupling (pyridazines)
3-6 Intramolecular arylation of amines (cyclic amines)
3-14 Intramolecular arylation of active-hydrogen compounds
3-17 Arylation of heterocyclic nitrogen compounds
3-18 Amination of heterocyclic nitrogen compounds
4-7 Cyclization of alcohols with lead tetraacetate (tetrahydrofurans)
4-15 Intramolecular arylation (Pschorr)
5-7 Addition of H_2S to conjugated diynes (thiophenes)
5-9 Addition of ammonia or primary amines to conjugated diynes (pyrroles)
5-12 Hydrogenation of heterocyclic aromatic rings
5-30 Photooxidation of dienes (cyclic peroxides)
5-33 1,3-Dipolar addition to double or triple bonds
5-34 Diels-Alder addition involving hetero atoms
5-37 Addition of nitrenes to dienes; expansion of heterocyclic rings upon treatment with carbenes
6-6 Reaction between 1,4-diketones and acids (furans)
6-12 Addition of H_2S to aldehydes or ketones (cyclic mercaptals)
6-14 Reaction between aldehydes and ammonia (cyclic amines)
6-15 Intramolecular addition of amines to carbonyl groups (cyclic imines)
6-21 Reaction between hydrazines and β-diketones or β-keto esters (pyrazoles; pyrazolones)
6-28 Reduction of N-alkylpyridinium salts (dihydropyridines)
6-35 Alkylation of salts of nitrogen heterocyclic compounds (cyclic amines)
6-51 Reaction between alcohols and aldehydes (dioxanes)
6-57 Trimerization of aldehydes (trioxanes)
6-58 Condensation of aldehydes with nitriles
6-59 Dimerization or trimerization of C=N compounds
6-61 Trimerization of nitriles (triazines)
6-63 Reaction between diazo compounds and sulfur (episulfides)
6-65 Addition of olefins to aldehydes or ketones (oxetanes)
8-16 Curtius rearrangement of cycloalkyl or aryl azides
8-27 Cyclization of arylhydrazones (Fischer indole synthesis)
8-32 Acid-catalyzed rearrangement of N-haloamines (pyrrolidines; piperidines—Hofmann-Löffler)
9-1 Aromatization of heterocyclic rings
9-2 Cyclodehydrogenation
9-34 Reduction of α,β-unsaturated ketones (pyrazolones)
9-36 Reduction of lactams (cyclic amines)
9-37 Reduction of lactones (cyclic ethers)
9-57 Intramolecular coupling of imines

Hydrates (*see gem*-Diols)

Hydrazides

0-51 Acylation of hydrazines with acyl halides
0-54 Acylation of hydrazines with esters

Hydrazines

3-18 Hydrazination of heterocyclic nitrogen compounds
5-9 Addition of hydrazines to olefins
8-15 Reaction between ureas and NaOBr (Hofmann)
9-44 Reduction of N-nitroso compounds
9-46 Reduction of azo compounds or diazonium salts
9-61 Reduction of nitro compounds

Hydrazo Compounds (*see* Hydrazines)

Hydrazones

2-6 Aliphatic diazonium coupling
6-21 Addition of hydrazines to aldehydes or ketones
9-11 Cleavage of double bonds with hydrazinium ion or diazonium salts

Hydroperoxides

0-31 Reaction between alkyl or acyl halides and hydrogen peroxide
2-15 Reaction between Grignard reagents and oxygen
4-8 Autoxidation
5-7 Addition of mercaptans to olefins in the presence of oxygen

Hydroxamic Acids

0-51 Acylation of hydroxylamine with acyl halides
0-54 Acylation of hydroxylamine with esters
6-4 Hydrolysis of aliphatic nitro compounds

Hydroxy Acids

0-11 Hydrolysis of lactones
3-20 Hydroxylation of aromatic acids
6-5 Hydrolysis of cyanohydrins
8-6 Rearrangement of benzils
8-7 Rearrangement of α,β-epoxy ketones (Favorskii)
9-62 Reaction between keto aldehydes and base

Hydroxy Aldehydes and Ketones

0-6 Hydrolysis of diazo ketones
1-31 Rearrangement of phenolic esters (Fries)
6-39 Condensation of aldehydes and/or ketones (aldol)
6-44 Condensation of formaldehyde with aldehydes or ketones (Tollens)
6-53 Condensation of aromatic aldehydes (benzoin)
8-4 Rearrangement of α-hydroxy aldehydes or ketones
8-6 Reaction between benzils and Grignard reagents
9-19 Oxidation of epoxides
9-58 Condensation of esters (acyloin)

Hydroxyamines and Amides

0-49 Amination of epoxides
3-28 Rearrangement of aryl hydroxylamines
4-5 Hydroxylation of amines

6-14	Addition of ammonia to aldehydes or ketones
6-15	Addition of amines or amides to aldehydes or ketones
6-35	Addition of Grignard reagents to oximes
8-28	Rearrangement of amino esters

Hydroxy Esters

0-26	Transesterification of lactones
6-32	Reaction between aldehydes or ketones, zinc, and α-halo esters (Reformatsky)
6-40	Condensation between esters and aldehydes or ketones
6-52	Addition of aldehydes to alkynyl ethers
8-6	Rearrangement of benzils by means of alkoxide ion
8-28	Rearrangement of esters

Hydroxy Ethers

0-22	Alcoholysis of epoxides

Hydroxylamines

5-9	Addition of hydroxylamine to olefins
6-28	Reduction of oximes
7-8	Cleavage of amine oxides (Cope)
9-22	Oxidation of primary amines
9-43	Reduction of nitro compounds

Hydroxy Mercaptans and Sulfides

0-36	Reaction between epoxides and NaSH
0-37	Reaction between epoxides and mercaptides
6-12	Addition of H_2S to aldehydes or ketones

Hydroxy Nitriles

0-88	Reaction between epoxides and cyanide ion
6-47	Addition of HCN to aldehydes or ketones

Hydroxy Sulfonic Acids

0-42	Reaction between epoxides and bisulfite ion
6-13	Addition of bisulfite ion to aldehydes or ketones

Imides (including Ureides)

0-51	Reaction between acyl halides and lithium nitride
0-52	Amination of anhydrides
0-57	N-Alkylation of imides
0-58	N-Acylation of amides or imides
5-9	Addition of imides to olefins
6-56	Addition of acids to nitriles
6-59	Dimerization and trimerization of isocyanates
6-70	Addition of N-halo amides to isonitriles
8-15	Reaction between amides and NaOBr (Hofmann)
8-16	Rearrangement of acyl azides in the presence of water (Curtius)

Imines

2-7	Reaction between active-hydrogen compounds and nitroso compounds
5-9	Addition of amines to triple-bond compounds
6-14	Addition of ammonia to aldehydes or ketones
6-15	Addition of amines to aldehydes or ketones
6-37	Addition of Grignard reagents to nitriles
6-45	Addition of ylides to nitroso compounds
8-16	Pyrolysis of alkyl or aryl azides
9-5	Dehydrogenation of secondary amines

Imino Esters (Imidates)

6-10	Alcoholysis of nitriles (Pinner)
8-31	From amides

Inorganic Esters

0-32	Reaction of alcohols or alkyl halides with inorganic acids or halides
3-8	Reaction between aryl halides and $POCl_3$
5-4	Addition of inorganic acids to olefins
9-33	Oxidation of trialkylboranes

Isocyanates

0-51	Reaction between amines and phosgene
0-58	Reaction between oxalyl chloride and unsubstituted amides
0-61	Alkylation or acylation of cyanate ion
5-10	Addition of cyanic acid to vinyl ethers
8-15	Reaction between amides and NaOBr (Hofmann)
8-16	Rearrangement of acyl azides (Curtius)
8-17	Rearrangement of hydroxamic acids (Lossen)
8-18	Addition of hydrazoic acid to carboxylic acids (Schmidt)
9-27	Oxidation of isonitriles

Isonitriles

0-50	Reaction between primary amines and chloroform
0-88	Reaction between alkyl halides and cyanide ion
7-33	Elimination of water from N-alkylformamides

Isothiocyanates

0-51	Reaction between amines and thiophosgene
0-61	Alkylation or acylation of thiocyanate ion
3-22	Reaction between diazonium salts and thiocyanate ion
6-20	Addition of amines to carbon disulfide

Isothiuronium Salts

0-36	Reaction between alkyl halides and thiourea

Ketals (*see* Acetals)

Ketenes

7-1 Pyrolysis of carboxylic acids
7-15 Dehydrohalogenation of acyl halides
7-23 Dehalogenation of α-halo acyl halides

Ketenimines

6-45 Reaction between phosphoranes and isocyanates
7-1 Dehydration of amides

Keto Acids, Aldehydes, and Esters (*see* Dicarbonyl Compounds)

Ketones (*see also* Dicarbonyl Compounds, Unsaturated Carbonyl Compounds, etc.)

0-2 Hydrolysis of *gem*-dihalides
0-7 Hydrolysis of vinyl ethers or ketals
0-26 Alcoholysis of enol esters
0-30 Reaction between enol esters and carboxylic acids
0-67 Reduction of diazo ketones
0-86 Alkylation of ketones
0-89 Reaction between acyl halides and organometallic compounds
0-90 Reaction between other acid derivatives and organometallic compounds
0-94 Reduction of β-keto sulfoxides
0-95 Reduction of β-keto alkylidene phosphoranes
0-98 Ketonic decarboxylation
1-14 Acylation of aromatic rings (Friedel-Crafts)
1-22 Reaction between aromatic rings and phosgene
1-27 Acylation of aromatic rings with nitriles (Hoesch)
1-31 Rearrangement of phenolic ethers (Fries)
1-42 Reaction between arylcarbinols and diazonium salts (Stiles-Sisti)
2-2 Rearrangement of hydroxy olefins
2-10 Alkylation of enamines followed by hydrolysis (Stork)
2-26 Decarboxylation of β-keto acids or esters
2-27 Cleavage of tertiary alkoxides
2-28 Replacement of a carboxyl group by an acyl group
2-29 Basic cleavage of β-diketones
3-14 Arylation of ketones
4-28 Decomposition of tertiary hypochlorites
5-3 Hydration of alkynes or allenes
5-6 Cyclization of olefinic acids
5-12 Reduction of phenols
5-13 Oxidation of boranes; hydrolysis of unsaturated boranes
5-15 Addition of ketones to activated olefins (Michael); addition of Grignard reagents to α,β-unsaturated ketones
5-16 Free-radical addition of aldehydes or ketones to olefins
6-2 Hydrolysis of imines, oximes, hydrazones, and other C=N compounds
6-4 Hydrolysis of secondary aliphatic nitro compounds (Nef)

6-34	Reaction between alkyllithiums and carbon monoxide
6-37	Addition of Grignard reagents to nitriles
7-1	Dehydration of 1,2-diols
7-26	Fragmentation of γ-amino or γ-hydroxy halides
7-28	Fragmentation of 1,3-diols or γ-amino alcohols
7-31	Fragmentation of certain ketoximes
7-34	Alkaline hydrolysis of nitrates
7-35	Pyrolysis of β-hydroxy olefins
7-36	Pyrolysis of allyl ethers
8-2	Rearrangement of glycols and related compounds (pinacol)
8-3	Ring expansion of certain hydroxyamines (Tiffeneu-Demyanov)
8-4	Acid-catalyzed ketone rearrangements
8-9	Homologization of aldehydes or ketones
8-15	Reaction between α-hydroxy or α-halo amides and NaOBr (Hofmann)
8-21	Cleavage of hydroperoxides
8-30	Rearrangement of vinyl ethers
9-3	Oxidation of secondary alcohols
9-8	Oxidative cleavage of glycols and related compounds
9-10	Ozonolysis of olefins
9-11	Oxidative cleavage of olefins
9-12	Oxidation of diarylmethanes
9-15	Bisdecarboxylation of malonic acids
9-16	Oxidation of activated methylene groups
9-21	Oxidation of olefins with noble-metal salts
9-34	Reduction of diketones or quinones

Lactams

0-53	Cyclization of amino acids
0-54	Reaction between lactones and ammonia or amines
5-9	Addition of lactams to olefins
6-66	Addition of ketenes to imines; addition of enamines to isocyanates
8-18	Reaction between cyclic ketones and hydrazoic acid (Schmidt)

Lactones

0-25	Cyclization of hydroxy acids
0-27	Cyclization of halo acids
5-6	Cyclization of olefinic acids
6-65	Addition of ketenes to aldehydes or ketones
8-20	Reaction between cyclic ketones and peroxy compounds (Baeyer-Villiger)
8-32	Rearrangement of N-halo amides
9-20	Oxidation of diols
9-38	Reduction of cyclic anhydrides

Mercaptals

5-7	Addition of mercaptans to alkynes
6-12	Addition of mercaptans to aldehydes or ketones

Mercaptans

0-11 Hydrolysis of thiol esters
0-36 Reaction of alkyl halides with NaSH; cleavage of isothiuronium salts
1-9 Sulfurization of aromatic compounds (Herz)
2-18 Reaction between Grignard reagents and sulfur
3-5 Reaction between aryl halides and NaSH
3-22 Reaction between diazonium salts and NaSH
5-7 Addition of H_2S to olefins
9-47 Reduction of sulfonyl halides
9-55 Reduction of disulfides

Metallocenes

2-21 Reaction between sodium cyclopentadienylide and metal halides

Monoesters of Dicarboxylic Acids

0-26 Equilibration of dicarboxylic acids and esters
6-10 Alcoholysis of cyano acids

Nitriles (*see also* Dicyano Compounds, Cyano Carbonyl Compounds, etc.)

0-86 Alkylation of nitriles
0-88 Reaction between alkyl halides and cyanide ion
1-28 Direct cyanogenation of aromatic rings
2-26 Decarboxylation of α-cyano acids
3-11 Reaction between aryl halides and CuCN (Rosenmund-von Braun)
3-12 Cyanide fusion of sulfonic acid salts
4-20 Reaction between diazonium salts and CuCN (Sandmeyer)
5-15 Addition to activated olefins (Michael)
5-16 Free-radical addition of nitriles to olefins
5-20 Addition of HCN to olefins
6-23 From aldehydes
6-42 From rhodanine
6-60 Reaction between acid salts and BrCN
7-30 Dehydration of aldoximes and similar compounds
7-31 Fragmentation of ketoximes
7-32 Dehydration of amides
9-5 Dehydrogenation of amines
9-48 Reduction of nitrile oxides

Nitro Compounds

0-59 Reaction between alkyl halides and nitrite ion
0-86 Alkylation of nitro compounds
0-91 Acylation of nitro compounds
1-2 Nitration of aromatic rings
1-33 Rearrangement of N-nitro aromatic amines
2-26 Decarboxylation of α-nitro acids
2-35 N-Nitration of amines or amides
3-17 Methylation of aromatic nitro compounds
4-12 Nitration of paraffins

4-19 Reaction between diazonium salts and sodium nitrite
5-15 Addition to activated olefins (Michael)
5-25 Addition of NOCl and other nitrogen compounds to olefins
5-32 Addition of N_2O_4 and other nitrogen compounds to olefins
6-41 Addition of nitro compounds to aldehydes or ketones
9-23 Oxidation of primary amines, oximes, or nitroso compounds

Nitroso Compounds

1-3 Nitrosation of aromatic rings
1-34 Rearrangement of N-nitroso aromatic amines (Fischer-Hepp)
1-40 Reaction between aromatic hydroxy acids and nitrous acid
2-7 Nitrosation at a carbon bearing an active hydrogen
2-35 Reaction between secondary amines or amides and nitrous acid
5-25 Addition of NOCl to olefins
5-32 Addition of N_2O_3 to olefins
9-7 Oxidation of hydroxylamines
9-22 Oxidation of primary amines

Olefins (*see* Alkenes)

Organometallic Compounds

2-12 Metalation of susceptible positions with organometallic compounds
2-13 Metalation of susceptible positions with metals or strong bases
2-14 Cleavage of alkyl groups from di- or polyvalent organometallic compounds
2-20 Reaction between an organometallic compound and a metal
2-21 Reaction between an organometallic compound and a metal halide
2-22 Reaction between an organometallic compound and an organometallic compound (exchange)
2-24 Metalation of alkyl or aryl halides with metals
2-25 Metalation of alkyl or aryl halides with organometallic compounds
5-39 Addition of organometallic compounds to olefins
8-13 Rearrangement of Grignard reagents

Ortho Esters

0-16 Reaction of alkoxides with 1,1,1-trihalides (Williamson)
0-21 Transetherification
6-6 Addition of alcohols to formic acid
6-9 Reaction between imino ester salts and alcohols

Ortho Thioesters

6-12 Addition of mercaptans to acyl halides

Osazones

6-21 Addition of hydrazines to α-hydroxy aldehydes or ketones

Oxime Ethers

0-19 Alkylation of oximes with diazo compounds
0-34 Alkylation of oximes with alkyl sulfates
5-5 Addition of oximes to olefins

Oximes

2-7	Nitrosation at a carbon bearing an active hydrogen
5-25	Addition of NOCl to olefins
6-22	Addition of hydroxylamine to aldehydes or ketones
8-32	Photolysis of nitrites (Barton)
9-22	Oxidation of aliphatic primary amines
9-51	Reduction of nitro compounds

Oxiranes (*see* Epoxides)

Ozonides

9-10	Ozonolysis of olefins

Peresters

0-31	Reaction of acyl halides with hydroperoxides

Peroxides (*see also* Hydroperoxides, Peresters)

0-31	Reaction of alkyl and acyl halides with sodium or hydrogen peroxide
4-9	Reaction between hydroperoxides and susceptible hydrocarbons
5-30	Photooxidation of dienes

Phenols

0-7	Acid cleavage of alkyl aryl ethers
0-11	Hydrolysis of phenolic esters
0-32	Cleavage of phenolic ethers with sulfonic acids
0-65	Cleavage of phenolic ethers with HI or HBr
0-83	Cleavage of aryl ethers with Grignard reagents
1-29	Electrophilic hydroxylation of aromatic rings
1-31	Rearrangement of phenolic esters (Fries)
1-32	Rearrangement of phenolic ethers
2-15	Reaction between aryl Grignard reagents and oxygen
3-1	Hydrolysis of aryl halides and other compounds
3-2	Reaction between naphthylamines and bisulfite ion (Bucherer)
3-3	Alkali fusion of sulfonates
3-20	Nucleophilic hydroxylation of aromatic acids
3-21	Hydrolysis of diazonium salts
3-28	Rearrangement of N-hydroxylamines
4-5	Free-radical hydroxylation of aromatic rings
6-27	Reduction of quinones
8-5	The dienone-phenol rearrangement
8-25	Rearrangement of allyl aryl ethers (Claisen)
8-33	Rearrangement of azoxy compounds (Wallach)
9-13	Oxidative cleavage of alkylbenzenes or aromatic aldehydes

Phosphines

0-44	Reaction between alkyl halides and phosphine
0-77	Reduction of quaternary phosphonium salts
2-21	Reaction between phosphorus halides and Grignard reagents

Phosphonates

6-45 Reaction between alkyl halides and phosphites

Phosphoranes

0-95 Acylation of phosphoranes
6-45 Treatment of phosphonium ions with alkyllithiums; addition of halocarbenes to phosphines

Quaternary Ammonium and Phosphonium Salts

0-44 Alkylation of amines (Menschutkin) or phosphines

Quinones

6-2 Hydrolysis of quinone imines
8-34 Oxidation of naphthoquinones (Hooker)
9-4 Oxidation of phenols or aromatic amines
9-18 Oxidation of aromatic hydrocarbons

Schiff Bases (*see* Imines)

Semicarbazones

6-21 Addition of semicarbazide to aldehydes or ketones

Sulfenyl Chlorides

4-11 Chlorosulfenation

Sulfides

0-37 Reaction between alkyl halides and mercaptides or Na_2S
1-9 Sulfurization of aromatic rings
2-18 Reaction between Grignard reagents and sulfur
3-5 Reaction between aryl halides or phenols and mercaptides or Na_2S
3-22 Reaction between diazonium salts and mercaptides or Na_2S
5-7 Addition of mercaptans to olefins
5-24 Addition of sulfenyl chlorides to olefins
7-12 Cleavage of sulfonium compounds
9-37 Reduction of thiol esters
9-49 Reduction of sulfoxides or sulfones
9-54 Reduction of disulfides

Sulfinic Acids

0-103 Reduction of sulfonyl chlorides
7-13 Cleavage of sulfones

Sulfonamides

0-57 N-Alkylation of sulfonamides
0-86 Alkylation of sulfonamides
0-91 Acylation of sulfonamides
0-101 Reaction between sulfonyl halides and ammonia or amines
3-14 Arylation of sulfonamides

5-9 Addition of sulfonamides to olefins
5-15 Addition of sulfonamides to activated olefins (Michael)
6-41 Addition of sulfonamides to aldehydes or ketones (Knoevenagel)
7-17 Cleavage of Michael adducts

Sulfones

0-41 Reaction between alkyl halides and sulfinates
0-86 Alkylation of sulfones
0-91 Acylation of sulfones
0-104 Reaction between sulfonic acid derivatives and Grignard reagents
1-10 Sulfonylation of aromatic rings
3-5 Reaction between aryl halides and sulfinates
3-14 Arylation of sulfones
5-15 Addition of sulfones to activated olefins (Michael)
5-24 Addition of sulfonyl halides to olefins
6-41 Addition of sulfones to aldehydes or ketones (Knoevenagel)
7-17 Cleavage of Michael adducts
9-28 Oxidation of sulfides or sulfoxides

Sulfonic Acid Esters

0-32 Reaction between alcohols or ethers and sulfonic acids
0-86 Alkylation of sulfonic acid esters
0-91 Acylation of sulfonic acid esters
0-100 Alcoholysis of sulfonic acid derivatives
1-30 Reaction between arylsulfonyl peroxides and aromatic rings
3-14 Arylation of sulfonic acid esters
5-4 Addition of sulfonic acids to olefins
5-15 Addition of sulfonic acid esters to activated olefins (Michael)
6-41 Addition of sulfonic acid esters to aldehydes or ketones (Knoevenagel)
7-17 Cleavage of Michael adducts

Sulfonic Acids

0-42 Reaction between alkyl halides and sulfite ion
0-99 Hydrolysis of sulfonic acid derivatives
1-7 Sulfonation of aromatic rings
1-41 Sulfonation with rearrangement (Jacobsen)
1-44 Migration of sulfo groups
2-8 Sulfonylation of aldehydes, ketones, or acids
3-5 Reaction between aryl halides or arylamines and sulfite ion
5-8 Addition of sodium bisulfite to olefins
9-24 Oxidation of mercaptans or other sulfur compounds

Sulfonium Salts

0-37 Reaction between alkyl halides and sulfides

Sulfonyl Halides

0-102 From sulfonic acid and derivatives
1-8 Halosulfonation of aromatic rings
4-11 Free-radical halosulfonation (Reed)

Sulfoxides

0-94	Reaction between esters and dimethyl sulfoxide carbanion
1-9	Sulfurization of aromatic rings with thionyl chloride
9-28	Oxidation of sulfides

Thioamides

1-15	Amidation of aromatic rings with isothiocyanates
6-36	Addition of Grignard reagents to isothiocyanates
9-64	Reaction of ketones with sulfur and ammonia or amines

Thiocarbamates

6-5	Hydrolysis of thiocyanates
6-8	Addition of alcohols to isothiocyanates

Thiocyanates

0-43	Reaction between alkyl halides and thiocyanate ion
3-5	Reaction between aryl halides and thiocyanate ion
3-22	Reaction between diazonium salts and thiocyanate ion

Thioethers (*see* Sulfides)

Thiol Acids and Esters

0-38	Reaction between acid derivatives and mercaptans or H_2S
1-27	Reaction between aromatic rings and thiocyanates
5-3	Hydration of acetylenic thioethers
5-7	Addition of thiol acids to olefins; addition of mercaptans to ketenes
5-18	Hydrocarboxylation of olefins in the presence of mercaptans
6-38	Addition of Grignard reagents to carbon disulfide

Thiols (*see* Mercaptans)

Thiones

6-12	Addition of H_2S to aldehydes or ketones

Thioureas (*see* Ureas)

Triazenes

1-4	Reaction between aromatic amines and diazonium salts
2-35	Reaction between amines and diazonium salts

Unsaturated Acids, Esters, Aldehydes, Ketones (*see* Unsaturated Carbonyl Compounds)

Unsaturated Alcohols and Phenols

6-41	Condensation of alkyne salts with aldehydes or ketones
6-51	Addition of aldehydes to olefins (Prins)
8-3	Ring opening of cycloalkyl carbonium ions
8-25	Rearrangement of allyl aryl ethers (Claisen)

Unsaturated Carbonyl Compounds

2-2	Isomerization of α-hydroxy alkynes
2-9	Acylation of olefins

5-15 Addition to activated alkynes (Michael)
5-18 Hydrocarboxylation of triple bonds
5-27 Addition of acyl halides to triple bonds
5-38 Carboxylation of halides with insertion of acetylene
6-17 Reaction between aldehydes, ammonia, and aldehydes, ketones, or esters (Mannich)
6-32 Reaction between aldehydes or ketones, zinc, and α-halo esters (Reformatsky)
6-39 Condensation of aldehydes and/or ketones (aldol)
6-40 Condensation between esters and aldehydes or ketones
6-41 Condensation between active-hydrogen compounds and aldehydes or ketones (Knoevenagel)
6-42 Condensation between anhydrides and aldehydes (Perkin)
6-45 Condensation between β-carboxy phosphoranes and aldehydes or ketones
6-52 Addition of aldehydes, ketones, esters, or amides to alkynyl ethers
7-3 Pyrolysis of lactones
8-5 The phenol-dienone rearrangement
8-7 Rearrangement of dihalo ketones (Favorskii)
8-25 Rearrangement of allyl vinyl ethers (Claisen)
8-26 Rearrangement of 3-hydroxy-1,5-dienes; rearrangement of vinylhydroxycyclopropanes
9-1 Dehydrogenation of 1,4-diones
9-16 Oxidation of a methylene group α to a double or triple bond

Unsaturated Nitriles, Nitro Compounds, and Sulfonic Esters

5-15 Addition to activated alkynes (Michael)
5-20 Addition of HCN to alkynes
5-25 Addition of nitryl chloride to triple bonds
6-41 Condensation between active hydrogen compounds and aldehydes or ketones (Knoevenagel)

Ureas and Thioureas

2-32 Cleavage of α,β-acetylenic amides with amide ion
6-3 Hydrolysis of isocyanates
6-18 Addition of amines to isocyanates or isothiocyanates
8-15 Reaction between amides and lead tetraacetate

Ureides (*see* Imides)

Urethanes (*see* Carbamates)

Vinyl Ethers (*see* Enol Ethers)

Vinyl Halides

5-1 Addition of hydrogen halides to triple bonds
5-22 Halogenation of alkynes or allenes
5-26 Addition of alkyl halides to triple bonds
5-27 Addition of acyl halides to triple bonds

6-26 Addition of PCl_5 to aldehydes or ketones
7-9 Cleavage of α-chloro tertiary nitro compounds

Xanthates

6-11 Addition of alcohols to carbon disulfide

Ylides (*see also* Phosphoranes)

2-12 Treatment of quaternary ammonium salts with organometallic compounds

Ynamines

7-14 Reaction between vinylidine dihalides and amide ion

Name Index

Abe, T., 539
Abell, P. I., 455, 570, 571, 578, 579
Abraham, M. H., 452
Abraham, R. J., 194
Abrahams, S. C., 23
Abrahamson, E. W., 839
Abramovitch, R. A., 162, 492, 510
Acke, M., 663
Acott, B., 817
Adam, J., 536
Adamcik, J. A., 300
Adams, D. G., 149
Adams, F. C., 155
Adams, J. T., 365
Adams, M., 897
Adams, R., 71, 73, 76, 78
Addy, J. K., 302
Adema, E. H., 412
Adeström, R., 807
Adkins, H., 592, 896
Adler, E., 866
Adolph, H. G., 878
Adrian, F. J., 156
Agadzhanyan, Ts. E., 851
Agnihotri, R. K., 598
Agtarap, A., 21
Ahmad, A., 666, 777
Ahmad, M., 105
Ahmberg, C. H., 557
Ahramjian, L., 701
Ahrens, H., 159
Akabori, S., 91
Akhrem, A. A., 651
Akhtar, M., 851
Akhtar, M. I., 579
Albright, J. D., 882
Alder, K., 603, 626, 630
Alderson, T., 603
Aldridge, C. L., 610
Alfrey, T., Jr., 433
Allabash, J. C., 351
Allan, Z. J., 501
Allen, A. D., 305
Allen, C. F. H., 627
Allen, G., 21, 64
Allen, J. C., 607
Allen, J. G., 495
Allen, R. G., 570, 571
Allen, R. H., 433
Allerhand, A., 65
Alleston, D. L., 348, 475
Allinger, J., 447
Allinger, N. L., 12, 101, 107, 109
Allred, A. L., 65
Allred, E., 266
Almenningen, A., 108
Almond, A. E., 207, 719
Altenkirk, B., 487
Altman, L. J., 49
Amiel, Y., 52, 194, 549
Amstutz, E. D., 772
Anbar, M., 534, 538, 612
Andersen, P., 156
Anderson, A. G., Jr., 345
Anderson, C. B., 545, 618
Anderson, D. H., 175
Anderson, D. R., 832
Anderson, E. W., 105, 135, 192
Anderson, G. J., 882
Anderson, G. W., 307, 338
Anderson, J. C., 429, 466
Anderson, J. D., 608
Anderson, J. E., 192
Anderson, K. K., 244
Anderson, R. S., 578, 898
Andersson, M., 472
Ando, W., 622
Andreades, S., 408, 676
Andrejević, V., 866
Andréu, P., 765
Andrews, L. J., 66, 261, 404
Andrussow, K., 221
Anet, F. A. L., 105, 121, 135, 161
Anet, R., 121
Angus, H. J. F., 637
Angus, J. C., 736
Angyal, S. J., 101, 107, 109, 869, 883
Ansell, M. F., 586
Anteunis, M., 663, 686
Antoniades, E. P., 820
Anzai, H., 441
Aoki, K., 618
Appel, R., 593, 645
Appelbaum, A., 546
Appl, M., 818
Applegate, L. E., 280
Applequist, D. E., 37, 142, 155, 254, 526
Aprahamian, N. S., 405
Arai, M., 538
Arbasino, M., 886
Arbuzov, B. A., 632, 705
Arbuzov, Yu. A., 621, 627
Archer, D. A., 759
Archer, S., 848

Arcus, C. L., 91, 783
Arens, J. F., 583, 665, 714, 872
Argabright, P. A., 342, 509, 764
Armanious, M. S., 812
Armstrong, R., 529
Arnett, E. M., 123, 221, 222, 224, 225, 438, 642
Arnold, R. G., 658
Arnold, R. L., 736
Arnold, R. T., 713, 746, 779, 842
Arnold, Z., 418
Arnstein, H. R. V., 206
Aroney, M., 104
Arthur, P., Jr., 610
Arundale, E., 712
Ash, A. B., 269
Ashby, E. C., 149–151, 471, 476, 686
Asinger, F., 910, 911
Askani, R., 119
Ašperger, S., 737
Asscher, M., 613
Astaf'ev, I. V., 454
Atkinson, V. A., 106
Aubrey, D. W., 757
Augdahl, E., 69
Augustijn, G. J. P., 439
Avakian, S., 493
Avison, A. W. D., 327
Avram, M., 67
Aycock, B. F., 570, 579
Aylward, F., 596
Ayrey, G., 737
Ayyangar, N. R., 600
Azizyan, T. A., 473

Baba, H., 3, 30
Babad, H., 353
Babayan, A. T., 760
Bachman, G. B., 559, 614, 819
Bachmann, W. E., 550, 788, 809
Backeberg, O. G., 684
Bacon, R. G. R., 504, 507, 857
Baddar, F. G., 428
Baddeley, G., 406, 413
Badding, V. G., 350
Bader, F. E., 423
Bader, J. M., 565
Bader, R. F. W., 160, 161, 317, 757
Badger, G. M., 39, 243, 557
Badiger, V. V., 279, 649
Baer, D. R., 800
Bafus, D. A., 149
Bailey, D. M., 811
Bailey, N. A., 55
Bailey, P. S., 857, 871, 872, 874
Bailey, W. C., Jr., 240
Bailey, W. J., 350, 751
Bailey-Wood, V. V., 428
Bainvel, J., 455
Baird, J. C., 196
Baird, M. D., 841
Baird, R., 135, 267
Baizer, M. M., 608
Baker, E. B., 126, 129
Baker, J. W., 56, 57, 286
Baker, K. M., 893
Baker, R., 259
Baker, R. H., Jr., 215
Baker, T. N., III, 614
Baker, W., 37, 45, 55
Bakinovskii, L. V., 616
Bakule, B., 226
Balaban, A. T., 412, 463, 616, 881
Balandin, A. A., 26, 755
Balasubramanian, A., 58
Balasubramanian, M., 106
Baldeschwieler, J. D., 188
Baldwin, F. P., 335
Baliga, B. T., 566
Ball, D. L., 865
Ball, W. J., 645
Ballester, M., 58, 404, 701
Baltazzi, E., 699
Baltzly, R., 333
Bamford, W. R., 763
Bamkole, T. O., 498
Ban, Y., 510
Banerjee, A. K., 550
Banholzer, K., 80
Bank, J., 334
Bank, S., 267, 454
Banks, D. F., 945
Banks, R. E., 632
Banoli, L., 833
Banthorpe, D. V., 430, 728, 738, 740, 741, 745, 754, 795, 828, 830
Barasch, W., 753
Barborak, J. C., 119
Barclay, L. R. C., 312, 409
Barfield, M., 187
Barker, I. R. L., 541, 865
Bârlădeanu, L., 348
Barlin, G. B., 228
Barltrop, J. A., 719
Barman, P., 122
Barnard, J. R., 861
Barnard, P. W. C., 305
Barnatt, A., 757
Barner, R., 830, 832
Barón, M., 717
Barrera, J., 405
Barron, B. G., 350
Barry, G. W., 225
Bartell, L. S., 23, 24, 216
Bartkus, E. A., 516

Bartlett, P. D., 124, 129, 145, 258, 267, 348, 619, 637, 640, 686, 783
Bartlett, R. S., 683, 898
Bartley, W. J., 121
Bartok, W., 889
Barton, D. H. R., 101, 544, 559, 579, 748, 751, 850, 851, 882
Basila, M. R., 65
Basolo, F., 76
Basselier, J., 67
Bassili, E., 908
Bassler, G. C., 167
Bastian, B. N., 265
Bastian, J., 903
Bastiansen, O., 33, 51, 108
Bastien, I. J., 126, 129
Bateman, L., 544
Bateman, L. C., 256, 257, 287
Batrakov, S. G., 895
Bauer, L., 575
Bauer, M., 317
Bauld, N. L., 507
Baumgarten, E., 380
Baumgarten, H. E., 815–817
Baumgarten, R. J., 883
Bautista, R. G., 105
Bayer, R. P., 884
Bayles, J. W., 230
Bayless, J. H., 411
Baylouny, R. A., 751
Beach, W. F., 561
Beard, W. Q., 517
Beaton, J. M., 850
Beck, B. H., 138
Becker, E. D., 187
Becker, E. I., 42, 356, 440, 686
Becker, H., 369, 698
Becker, W. E., 150, 471
Beckham, L. J., 613
Beckler, J. D., 475
Beckwith, A. L. J., 817, 850
Bedford, A. F., 26
Bedford, G. R., 820
Beers, M. J., 533
Beevers, C. A., 167
Beezer, A. E., 53
Behr, L. C., 851
Behrman, E. J., 539
Beirne, P. D., 732
Bel'chikova, F. A., 513
Belen'kii, L. I., 119, 120, 234, 557
Beletskaya, I. P., 451, 473
Belikov, V. M., 93
Bell, A., 637
Bell, F., 390
Bell, H. M., 137
Bell, J. A., 161, 466, 468, 643
Bell, R. P., 217, 221, 226, 457, 459, 655, 656
Bellamy, L. J., 175, 179, 180
Bellis, J. M., 170
Belov, B. I., 399, 484, 514, 553
Bender, M. L., 205, 215, 274, 276–278, 289, 308, 312–315, 335
Ben-Efraim, D. A., 52, 194
Beneš, M. J., 361
Benfy, O. T., 256
Bengelsdorf, I. S., 720
Benjamin, B. M., 291
Benkeser, R. A., 468, 469, 592, 598, 599
Bennett, C., 550
Bennett, M. A., 66
Bennett, R. P., 400
Benning, W. F., 675
Ben-Shoshan, R., 579
Benson, R. E., 54, 158
Benson, S. W., 24, 155, 160, 161, 455, 571, 580, 581, 748
Bent, H. A., 10, 21, 58
Bentley, K. W., 167, 168, 758
Bentley, R., 206
Benton, F. L., 872
Bentrude, W. G., 526
Berasconi, C., 490
Berchtold, G. A., 637
Berezovskii, G. A., 439
Bergel'son, L. D., 571, 707, 895
Berger, A., 221
Berger, C. R. A., 893
Berger, J. G., 165, 466, 766
Berger, M., 871
Berglund, C., 472
Berglund-Larsson, U., 378
Bergman, E., 648
Bergman, R. G., 137
Bergmann, E., 888
Bergmann, E. D., 604
Bergson, G., 454
Berkheimer, H. E., 225
Berkoff, C. E., 192
Berkowitz, J., 149
Berkowitz, W. F., 816
Berlin, A. J., 105, 192
Berlin, K. D., 323, 363
Berliner, E., 240, 376, 404, 414, 497
Berlo, R. C., 593, 897
Berman, J. D., 560
Bernardi, L., 712
Berneis, H. L., 744
Bernstein, H. I., 784
Bernstein, H. J., 182, 192
Bernstein, R. B., 736
Bernstein, S. C., 688
Berrigan, P. J., 300
Berry, R. S., 33, 493
Bersin, T., 863
Bersohn, R., 196

Berson, J. A., 137, 791, 795, 835
Bertelli, D. J., 45
Bertelson, R. C., 122
Berther, C., 884
Berti, G., 308
Best, P. A., 870
Bestmann, H. J., 649, 657, 704, 707, 708, 809
Bethell, D., 125
Beumel, O. F., Jr., 681
Bevan, C. W. L., 309, 498
Bevington, J. C., 717
Beyerman, H. C., 307
Beynon, J. H., 196
Bhacca, N. S., 182
Bhatia, Y. R., 272
Bhatt, M. V., 766
Bickel, A. F., 545, 578
Bickel, H., 423
Bicknell, R. C., 750
Bieber, J. B., 827
Biechler, S. S., 314
Biemann, K., 196–198
Biethan, U., 843
Bigley, B. D., 479, 719
Bijvoet, J. M., 83, 167
Bikales, N. M., 686
Bilevitch, K. A., 476
Billenstein, S., 360
Billups, W. E., 455
Bingham, K. D., 620
Binsch, G., 625
Biordi, J., 316
Biranowski, J. B., 736
Birch, A. J., 597
Birchall, J. M., 506
Bird, C. W., 608, 609
Birmingham, J. M., 474
Birnbaum, G., 19
Bishop, C. A., 746
Biskup, M., 54
Biss, J. W., 684
Bissell, E. R., 611
Bissing, D. E., 705
Black, D. K., 833
Blackman, S. W., 333
Blackwell, J., 349
Blackwood, R. K., 300
Blade-Font, A., 705
Blades, A. T., 750
Blair, J. S., 656
Blanchard, E. J., 335
Blanchard, E. P., 648
Blatt, A. H., 428
Blattner, H. M., 676
Blicke, F. F., 670
Bliss, A. D., 775
Blomberg, C., 92, 150
Blomquist, A. T., 51, 80, 122, 712, 789
Bloomfield, J. J., 367, 709, 904
Blues, E. T., 349
Bluhm, A. L., 871
Blukis, V., 23
Blum, J., 560
Bly, R. S., 267, 793
Boatman, S., 299
Böck, F., 654
Bock, H., 400
Bockemüller, W., 342
Bodendorf, K., 774
Bodot, H., 576
Boekelheide, V., 53
Bogdanov, G. N., 802
Bogdanova, A. V., 585
Bogomol'nyi, V. Ya., 531
Boguslavskaya, L. S., 549
Bohlmann, F., 172, 437, 575
Bohm, B. A., 570
Bokhoven, C., 167
Böll, W. A., 54, 763
Bollinger, J. M., 123, 642
Bollyky, L., 595, 764
Bolon, D. A., 267
Bolton, R., 562
Bond, G. C., 595
Bonelli, R. A., 498
Bonham, R. A., 23
Bonhoeffer, K. F., 909
Bonner, W. A., 793
Bontekoe, J. S., 307
Bonthrone, W., 865
Boord, C. E., 117
Booth, H., 759
Booth, W. T., Jr., 363
Boozer, C. E., 205, 269, 535
Borchert, A. E., 837
Borchert, E. E., 405
Borčić, S., 140, 267
Bordwell, F. G., 192, 471, 571, 623, 736, 769, 770, 847, 901
Borgardt, F. G., 622
Borgulya, J., 830
Borgwardt, S., 289
Borisov, A. E., 147
Borkowski, M., 235
Borowitz, I., 807
Bos, H. J. T., 714
Bosch, H. W., 75
Boschan, R., 778
Bose, A. N., 580, 581, 748
Boskin, M. J., 356
Bothner-By, A. A., 52, 194, 812
Bott, K., 291
Bott, R. W., 379
Bottaccio, G., 649
Botteron, D. G., 752
Boudakian, M. M., 279, 280, 569

Bourns, A. N., 215, 435, 737, 757, 779
Bovey, F. A., 105, 192
Bowden, K., 224, 590
Bowers, A., 611
Bowers, J. E., 811
Boyce, C. B., 106
Boyer, J. H., 341
Brachel, H. von, 603
Brackman, W., 866
Bracudlin, H. P., 119
Bradley, A., 538
Bradley, J. N., 164, 721, 811
Bradley, W., 510
Bradshaw, J. S., 637
Brady, J. D., 380
Braendlin, H. P., 403
Bragole, R. A., 833
Brain, D. K., 548
Bram, G., 366
Brand, J. C. D., 168, 402
Brandenberger, S. G., 433, 876
Brandon, R. W., 159
Brandsma, L., 329
Brannock, K. C., 603, 637, 638
Brasen, W. R., 888
Bratolyubov, A. S., 534
Braude, E. A., 147, 168, 174, 273, 590, 861
Braun, A., 614
Braun, A. M., 733
Brechbühler, H., 324
Bredenberg, J. B., 190
Breder, C. V., 411
Bregman, J., 53
Brenneisen, P., 774
Breslow, D. S., 595
Breslow, R., 43, 49, 50, 52, 736, 800, 806
Breuer, E., 591
Brewer, R. G., 25
Brewer, W., 536
Brewster, J. H., 86, 361, 826
Brickman, M., 386
Briegleb, G., 67
Brieux, J. A., 498
Briggs, L. H., 167
Brill, W. F., 284, 621
Brindell, G. D., 791
Briody, J. M., 274
Brizzolara, A., 464
Broaddus, C. D., 469
Broch, N. C., 413
Brockway, L. O., 59, 198
Brodhag, A. E., 888
Brodskii, A. I., 539
Brois, S. J., 332
Bromham, N. H., 847
Brooke, G. M., 495
Brookhart, M., 135
Broome, J., 679
Brower, K. R., 783
Brown, B. R., 435, 478, 679
Brown, C. A., 592
Brown, D. F., 750
Brown, H. C., 20, 130, 131, 137, 222, 228, 229, 234–236, 240, 351–353, 380, 381, 388, 391, 392, 394, 395, 409, 411, 433, 471, 474, 527, 556, 582, 591–593, 599, 600, 678–681, 684, 739, 741–744, 766, 791, 814, 889, 891, 893, 895, 902
Brown, J. M., 146, 835
Brown, M. G., 23, 33
Brown, M. S., 896
Brown, R. A., 659
Brown, R. D., 382
Brown, R. F., 18
Brown, R. K., 845
Brown, T. L., 58, 149, 193
Brown, W. G., 593, 678
Brownell, R., 864
Brownlie, G., 797
Brownstein, S., 182, 430
Bruckenstein, S., 218, 222
Bruckner, V., 235
Bruice, T. C., 276, 278, 339
Brunie, J., 456
Bruson, H. A., 568, 585, 588, 590, 604
Bryan, R. F., 120
Bryant, D. R., 299
Bryce-Smith, D., 349, 355, 411, 469, 509, 637
Brydon, D. L., 552
Bublitz, D. E., 434
Buchanan, G. L., 480
Büchi, G., 878
Büchi, H., 324
Büchner, O., 645
Büchner, W., 593
Buchta, E., 360
Buck, C. J., 789
Buck, J. S., 714
Buckler, S. A., 332
Buckles, R. E., 565, 611
Buckley, N. C., 584
Buckschewski, H., 657
Budde, W. L., 443, 583
Budzikiewicz, H., 196, 197, 685
Buehler, C. A., 426
Buess, C. M., 40
Buist, G. J., 869
Bumgardner, C. L., 350, 517
Bunbury, H. M., 913
Bunce, S. C., 410
Buncel, E., 779, 851
Bunds, J., 559
Bunnett, J. F., 206, 226, 287, 338, 435, 440, 483, 488–490, 492–494, 498, 499, 502, 507, 515, 519, 520, 728, 737

Bunton, C. A., 137, 216, 251, 257, 305, 430, 620, 868, 869
Bunyan, P. J., 907
Burawoy, A., 64
Burckhalter, J. H., 672
Burckhardt, U., 494
Burdett, J. L., 192
Burdge, D. N., 557
Burditt, A. M., 207, 719
Burdon, J., 495
Burgard, A., 816
Burger, T. F., 761
Burgert, 425
Burgmaster, J., 438
Burgstahler, A. W., 352
Burham, R. L., 611
Burkett, H., 435
Burkoth, T. L., 54
Burkus, T., 369
Burlingame, A. L., 458
Burlitch, J. M., 466, 644
Burnelle, L., 14, 565
Burness, D. M., 477
Burpitt, R. D., 603, 637, 638
Burrous, M. L., 598
Burton, H., 125
Burton, P. E., 790
Burwell, R. L., Jr., 344, 594, 595, 682
Bushweller, C. H., 106
Bussell, G. E., 206
Butler, A. R., 309
Butskus, P. F., 568, 626
Buttenberg, W., 812
Buttery, R. G., 164
Butz, L. W., 626
Buu-Hoï, N. P., 389, 440
Buzbee, L. R., 500
Bykhovskaya, M. Sh., 569

Cadogan, J. I. G., 529, 552, 570, 607, 643, 907
Caglioti, L., 894
Cahn, R. S., 84
Cain, M. E., 328
Cairns, T. L., 561, 574, 644, 665
Cais, M., 66, 612
Calder, I. C., 54, 194
Caldin, E. F., 64
Callahan, F. M., 307
Camara, B. R., 619
Campaigne, E., 665
Campbell, A., 783
Campbell, B. K., 690
Campbell, B. N., Jr., 408
Campbell, J. R., 501
Campbell, K. N., 690
Campbell, T. W., 718
Cantacuzène, J., 667
Canter, F. C., 341
Canterino, P. J., 642
Capell, L. T., 924
Capon, B., 263
Cardy, D. E., 459
Caress, E. A., 742
Carey, F. A., 768
Carey, J. G., 512
Carges, G. L., 788
Cargill, R. L., 119
Carlin, R. B., 788, 830
Carlsmith, L. A., 492, 493, 497
Carmack, M., 328, 910
Carpenter, J. G. D., 12
Carpino, L. A., 347
Carrington, A., 196
Carroll, S., 559
Carter, F. L., 49, 121
Carter, G. B., 429
Carter, H. E., 699
Carter, J. C., 759
Carter, P., 267
Casadevall, A., 221
Casanova, J., Jr., 93, 879
Casapieri, P., 261
Caserio, M. C., 317, 492, 639
Casey, C., 21
Casnati, G., 419
Cason, J., 343, 362, 688, 691, 865
Caspar, M. L., 790
Cassar, L., 650
Cassis, F. A., 411
Cast, J., 827
Castaner, J., 404
Castle, M. A., 192
Castner, R. C., 866
Castro, C. E., 507, 592
Casy, A. F., 333
Cauquil, G., 221
Cauquis, G., 67
Cava, M. P., 481, 525
Cawley, J. J., 662
Cazes, J., 530, 552
Ceccon, A., 261
Cecere, M., 400, 614
Čekovič, Z., 542
Cerfontain, H., 402, 439
Červinka, O., 690
Chalfont, G. R., 552
Challis, B. C., 485
Chamberlain, N. F., 189
Chambers, R. A., 346
Chambers, R. D., 426
Chambers, V. C., 235
Chamness, J. T., 830
Chan, S. I., 109
Chan, T., 826
Chandler, G. S., 438
Chang, F. C., 373

Chang, H. W., 43, 49, 50, 52
Chang, S., 259
Chang, Y., 874
Chang, Y. W., 864
Chang Kuo, M. C., 627
Chapman, N. B., 494, 498
Chaput, E. P., 690
Charles, G., 698
Charles, K. R., 225
Charles, R., 93
Charles-Sigler, R., 93
Charman, H. B., 445, 446
Charpentier-Morize, M., 165, 807
Charton, M., 239, 240
Chatt, J., 66, 582
Chaudhuri, N., 164
Chaykovsky, M., 369, 649, 703, 721
Chekulaeva, I. A., 569, 590
Chen, A., 143, 222
Chen, M. C., 308, 312
Chérest, M., 291, 650, 800
Chernick, C. L., 611
Chesnut, D. B., 54
Cheuychit, P., 557
Chiang, Y., 225, 382
Child, W. C., Jr., 70
Chilingaren, A., 801
Chiltz, G., 534
Chinoporos, E., 158
Chiola, V., 284
Chiu, J., 662
Chiusoli, G. P., 649, 650
Chivers, T., 143, 222
Chloupek, F. J., 130, 137, 277
Chodkiewicz, W., 550
Choguill, H. S., 440
Choi, S. U., 411
Chollar, B., 841
Chortyk, O. T., 822
Chow, Y., 277
Christen, M., 382
Christian, D. T., 455
Christie, K. O., 504
Christman, D. R., 372
Christmann, A., 162
Christmann, K. F., 705
Chuchani, G., 411
Chung, B. C., 344
Ciganek, E., 647, 762, 844
Cilento, G., 16
Cimatoribus, L., 428
Ciuffarin, E., 222
Ciula, R. P., 119
Claisen, L., 273, 833
Claisse, J. A., 588
Clar, E., 39, 40
Clardy, J., 493
Clark, G. W., 199, 645
Clark, J., 228
Clark, R. F., 677
Clarke, L., 438
Clarke, R. L., 105
Clarkson, D., 28
Clausius, K., 845
Clayton, J. W., 269
Clément, G., 901
Clement, R. A., 58
Clement, W. H., 884
Cleveland, F. F., 181, 182
Clifford, A. A., 550
Clippinger, E., 136, 259
Closs, G. L., 159, 165, 332, 647, 763
Closs, L. E., 763
Closson, W. D., 139, 267
Clunie, J. C., 655
Coates, G. E., 148, 442, 470
Coburn, J. F., Jr., 646
Cocivera, M., 735
Cockerill, A. F., 737
Coe, G. R., 475
Coe, P. L., 495
Coffman, D. D., 678
Cohen, H. M., 475
Cohen, M., 863
Cohen, M. D., 641
Cohen, S. G., 560, 883
Cohen, T., 508, 882
Cohn, M., 655
Coke, J. L., 732, 759
Colard, P., 165
Cole, A. R. H., 175
Cole, R. S., 551
Cole, T., 155
Cole, T. W., 119
Cole, W. J., 459
Coles, J. A., 147
Collins, C. H., 566, 751
Collins, C. J., 206, 291, 798
Collins, G. R., 511, 546
Collis, M. J., 612
Colonge, J., 456
Colter, A., 137
Combes, C. M., 648
Comisarow, M. B., 126–129, 135, 136, 138, 193, 258
Condon, F. E., 230, 348, 381, 407
Conia, J. M., 808
Conley, R. T., 777, 822
Connolly, J. W., 70
Connor, T. M., 193
Conroy, H., 182, 189, 831
Cook, A. H., 913
Cook, C. E., 721
Cook, D., 415
Cook, J. W., 43
Cook, M. J., 660
Cooke, G. A., 312
Cooke, M. P., Jr., 732, 759

Cookson, R. C., 50, 101, 609, 628, 779, 806
Coombs, R. V., 360
Cooper, G. D., 770, 815
Cooper, K. A., 287, 734, 746, 747
Coops, J., 92
Cope, A. C., 80, 96, 120, 190, 254, 357, 543, 758, 760–762, 789, 790, 793, 834, 842, 878, 904
Corbett, G. E., 427
Corbett, J. F., 505
Cordes, E. H., 238, 658
Corey, E. J., 93, 148, 187, 369, 593, 622, 649, 703, 721, 724, 768, 796, 879, 880
Corey, G. C., 870
Corey, H. S., Jr., 704
Corley, R. C., 721
Cornforth, J. W., 769
Cornforth, R. H., 769
Cornille, M., 14
Correia, J. S., 343
Corriu, R., 221, 413
Cosgrove, W. R., Jr., 70
Costain, C. C., 21
Cotter, R. J., 319
Cotton, F. A., 43
Cottrell, T. L., 21, 24
Coulson, C. A., 3, 28, 32, 33, 117
Cousins, L. R., 65
Coussemant, F., 669
Coverdale, A. K., 296
Coverdale, C. E., 291
Cowan, D., 475
Cowan, D. O., 151
Cowell, G. W., 721
Cowdrey, W. A., 252, 315, 553
Cox, B. G., 541
Cox, J. D., 27
Cox, O., 901
Coyle, J. J., 647
Crabbé, P., 110, 114
Craig, C. A., 675
Craig, J. C., 411, 483, 883
Craig, R. A., 117
Cram, D. J., 42, 90, 131, 132, 142, 147, 148, 218, 222, 292, 442, 447, 448, 454, 733, 739, 762, 764, 784, 786, 787, 793, 798, 815, 825, 893, 904
Crampton, M. R., 489
Crane, E. J., 932, 953
Craven, J. M., 58
Crawford, M., 699, 700
Crawford, R. J., 267, 300
Crawford, V. A., 56
Creswell, C. J., 65
Criegee, R., 50, 119, 823, 838, 857, 868, 869, 872, 874
Crisafulli, M., 419
Cristol, S. J., 559, 729, 731, 753, 772, 791
Crocker, H. P., 423
Crombie, L., 94
Cross, A. D., 175, 180
Crounse, N. N., 417
Crovatt, L. W., 427
Crowell, T. I., 666, 737
Cruickshank, D. W. J., 39
Cruickshank, P. A., 480
Crutchfield, M. M., 865
Cullen, E., 516
Cullinane, N. M., 428, 429
Cullis, C. F., 541, 857
Culvenor, C. J., 770
Cummings, T. F., 672
Cupas, C. A., 126, 128, 139
Curci, R., 887
Curl, R. F., Jr., 23
Curtin, D. Y., 147, 300, 441, 748, 759, 790, 812
Cusack, N. J., 893
Cuscurida, M., 350
Cuts, H., 119
Cvetanović, R. J., 161
Cywinski, N. F., 607
Czekalla, J., 67

Dacons, J. C., 878
Daeniker, H. U., 481
Dahlgren, G., Jr., 65
Dahm, R. H., 541
Dahn, H., 306
Daignault, R. A., 896, 899
Dailey, B. P., 23, 182
Dale, J., 109, 123, 454
Dale, W. C., 644
Dallinga, G., 453
Damico, R., 813
Dance, J., 628
Dangl, J. R., 180
Daniel, H., 761
Daniels, R., 575
Danilkina, L. P., 646
Dankner, D., 455
Dannley, R. L., 427
D'Arcy, R., 774
Da Re, P., 428
Dar'eva, E. P., 349, 682
Darrin, M., 880
Darwish, D., 738
Datta, A. P., 416
Daub, G. H., 696
Dauben, H. J., Jr., 43, 45, 535, 536
Dauben, W. G., 101, 119
Daughhetee, P. H., Jr., 886
Davidson, D. W., 655
Davidson, N., 155
Davidson, R. S., 527
Davies, A. G., 312, 890
Davies, D. I., 588, 878
Davies, D. S., 553

Davies, D. W., 37
Davies, W., 770
Davis, B. A., 162
Davis, B. R., 893
Davis, D. R., 187
Davis, G. T., 244, 338
Davis, J. A., 559
Davis, M., 105, 680
Davis, R., 370
Davis, R. A., 611
Davis, R. E., 769
Dawson, L. R., 224
Day, A. C., 719
Day, A. R., 681
Day, J. H., 41
Day, R. A., Jr., 170
Dayagi, S., 361
Dean, F. H., 611
Deans, F. B., 393
Dear, R. E. A., 439
DeBoer, C. D., 528, 536, 837
Deem, M. F., 680
De Feo, R. J., 338
DeFoe, J. D., 899
DeGroot, A., 37
de la Mare, P. B. D., 270, 284, 376, 381, 390, 396, 399, 403, 431, 562, 564, 574, 611, 739
de Ligny, C. L., 93
de Maheas, M., 418
Dembinski, J. W., 862
De More, W. B., 160, 161
DeMott, D. N., 535
Dem'yanov, N. Ya., 121
Dence, C. W., 438
Den Hertog, H. J., 527
Denney, D. B., 354, 356, 426, 472, 546, 561, 792
Denney, D. Z., 472, 546, 792
Deno, N. C., 125, 127–129, 221, 222, 224, 225, 243, 567, 584, 773, 855
DePuy, C. H., 65, 286, 657, 731, 733, 746, 747, 751, 756, 764
Derbentsev, Y. I., 755
Derfer, J. M., 117
Dermer, O. C., 533, 538, 550
Desai, N. B., 703
DeSelms, R. C., 648
Desmond, K. M., 536
Dessy, R. E., 143, 151, 222, 442, 443, 451, 475, 583
de Stevens, G., 676
DeTar, D. F., 156, 524, 530, 551
de Vijlder, J. J. M., 93
de Vries, K. S., 349, 354
de Vries, L., 119
Dewar, M. J. S., 19, 33, 46, 49, 56, 58, 67, 68, 427, 429, 564, 566, 580, 828
Dewey, R. S., 596
DeWolfe, R. H., 270, 271, 284
Deyrup, A. J., 129
Dhar, M. L., 744, 746
D'Hollander, R., 686
Diaper, D. G. M., 687, 871, 872
Diaz, A. F., 259
Dick, C. R., 459, 814
Dickens, B., 51
Dickerhoof, D. W., 149
Dickerman, S. C., 530, 551, 552, 554
Dickerson, D. R., 504
Dickinson, C. L., 574
Diebold, J. L., 808
Dieckmann, J., 605
Diehl, P., 188
Diêp, B. K., 389
Dietrich, M. A., 574
Dilling, W. L., 119
Dillon, R. C., 222
DiPietro, J., 607
Dittmer, B., 148
Dittmer, H., 269
Dixon, J. A., 509
Dixon, W. T., 539
Djerassi, C., 110, 112, 113, 115, 196, 197, 535, 769, 863, 894
Dobbs, H. E., 648
Dobinson, F., 872
Dobler, M., 54
Dodge, R. P., 51
Doering, W. von E., 43, 44, 119, 145, 164, 165, 254, 454, 466, 467, 644, 646, 647, 803, 823, 833, 834, 836, 842, 843, 879
Dolby, L. J., 712
Doleschall, G., 322
Dolfini, J. E., 569
Dombrovskii, A. V., 553, 615
Donaruma, L. G., 821, 822
Donath, W. E., 109
Donoghue, E., 638
Donzel, A., 306
Dorfman, E., 823
Dorfman, L., 638
Dornow, A., 762
Dorofeenko, G. N., 418, 463
Dostrovsky, I., 783
Douglas, A. W., 193
Douglas, D. E., 207, 719
Douglass, D. C., 135
Douglass, J. E., 433
Douglass, M. L., 471
Douwes, H. S. A., 412
Dowd, S. R., 465, 644
Dowd, W., 741
Doyarenko, M. N., 121
Drahowzal, F. A., 406, 408
Drake, N. L., 500
Draper, J. D., 318
Dreiding, A. S., 449

Drenth, W., 583, 725
Dresdner, R. D., 716
Druelinger, M. L., 23
Druey, J., 826
D'Silva, R. M., 751
Dubini, M., 650
DuBois, A. S., 424
Dubois, J. E., 574, 576
Dubrova, L. N., 430
Dudek, G. O., 193
Dudinskaya, A. A., 626
Duffey, D. C., 269, 479
Duffin, H. C., 548
Duffner, P., 708
Duffy, J. A., 315
Duhamel, P., 667
Dulova, V. G., 49
Duncan, A. B. F., 168, 175, 181
Duncan, F. J., 161
Dunitz, J. D., 54, 109, 120
Dunlop, A. K., 70
Dunnavant, W. R., 299, 696
Dunning, J. E., 759
Durham, L. J., 874
Dürr, H., 627
Durrell, W. S., 716
Durrett, L. R., 163
Durst, T., 95
Dutler, H., 797
Duynstee, E. F. J., 295
Dvoretzky, I., 163, 164, 876
Dvornikoff, M. N., 888
D'yachenko, A. I., 513
D'yachkovskii, F. S., 355
D'yakanov, I. A., 646
Dybvig, D. H., 300
Dyckes, D., 135
Dyer, J. R., 168, 173

Eaborn, C., 285, 379, 386, 393, 396
Eastham, A. M., 222
Eastham, J. F., 803
Eastman, R. H., 538
Eaton, P., 630
Eaton, P. E., 119
Ebel, H. F., 494
Eberhardt, M., 802
Ebersberger, J., 408
Eberson, L., 135
Ebner, C. E., 733
Eccles, J., 207, 719
Eddy, R. W., 261
Edgington, D. N., 293, 326
Edison, D. H., 731, 738
Edmison, M. T., 533, 538, 550
Edmondson, P. B., 26
Edmunds, F. S., 836
Edward, J. T., 896
Edwards, A. G., 833
Edwards, B. E., 665
Edwards, B. F. R., 428
Edwards, J. O., 287, 865
Edwards, O. E., 141
Edwards, W. R., Jr., 363, 414
Effenberger, F., 416
Efros, L. S., 39, 886
Egger, K. W., 155, 455, 571
Eggers, H., 708
Eglinton, G., 549
Eguchi, S., 690
Eholzer, U., 778
Ehrenson, S., 35, 238, 244
Ehrhart, G., 508
Eicher, T., 49
Eichler, S., 642
Eigenmann, E. W., 746
Eisch, J. J., 650
Eisenthal, R., 538, 881
Eisert, M., 163
Eisert, M. A., 648
Eistert, B., 370, 721, 809, 810
Eiter, K., 705
El-Abbady, A. M., 428
Elad, D., 606
Elam, E. U., 667
Elhafez, F. A. A., 90
Elia, R. J., 269
Elian, M., 881
Eliel, E. L., 12, 71, 83, 86, 90, 93, 101, 104, 107, 109, 110, 129, 142, 155, 192, 207, 236, 350, 361, 523, 551, 651, 681, 896
Elkobaisi, F. M., 429
Ellinger, C. A., 333
Elliot, R. D., 269
Ellis, R. J., 841
Ellsworth, R. L., 792
Elvidge, J. A., 673
Emerson, G. F., 51, 66
Emerson, M. T., 64
Emerson, W. E., 668
Emery, E. M., 899
Emmett, P. H., 596
Emmons, W. D., 486, 823, 885
Empedocles, P. B., 17
Eng, F. S., 649
Engel, G., 843
Engel, R. R., 467, 645, 646
Engelhardt, V. A., 677
Engelsma, J. W., 533
England, D. C., 574, 610, 676
English, J., Jr., 775
Englund, B. E., 561
Ennis, B. C., 423
Entwhistle, I. D., 764
Erickson, R. E., 878
Erivanskaya, L. A., 505

Erley, D. S., 433
Érmanson, A. V., 473
Erokhina, L. L., 642
Ershov, V. V., 379, 802
Erstein, W. W., 882
Erusalimskii, B. L., 531
Eschenmoser, A., 324, 864
Ess, R. J., 557
Esselen, G. J., Jr., 438
Euranto, E., 716
Evans, E. A., 363
Evans, E. R., 833
Evans, G. L., 665
Evans, J. C., 126, 398
Evans, M. B., 328
Evans, R. J., 877
Evans, R. J. D., 272
Evans, R. M., 857
Evans, T. W., 866
Evans, W. L., 225

Fabian, J., 665
Fabian, W., 827
Fabienke, E., 374
Fábryová, A., 690
Fahey, D. M., 480
Fahey, R. C., 216, 565, 566
Fahrenholtz, S. R., 742
Fainberg, A. H., 259, 296, 297
Fainzil'berg, A. A., 158, 535
Falbe, J., 945
Falkehag, I., 866
Fanta, P. E., 374, 507, 508
Farah, B. S., 677
Farber, M., 879
Farnum, D. G., 636, 723
Faro, H. P., 559
Farrar, M. W., 323, 888
Fava, A., 261, 373
Favorskii, A., 801
Fawcett, F. S., 678
Fedder, J. E., 341
Fedor, L. R., 276
Fedorova, A. V., 578, 584
Fehnel, E. A., 328
Feibush, B., 93
Feig, G., 546
Feigl, F., 439
Feldkimel, M., 353
Feldman, A., 89
Felix, A. M., 551
Felkin, H., 93, 291, 650, 800, 899
Feltkamp, H., 192
Felton, E. G., 767
Feng, M. S., 215
Fenselau, A. H., 882
Ferguson, G., 37
Ferguson, J. W., 788
Ferguson, L. N., 382, 877
Ferland, J. M., 896
Fernandez, J., 109
Fernandez, J. E., 672
Fernandez, V. P., 682
Ferrier, B. M., 843
Ferris, A. F., 777
Ferstandig, L. L., 65, 830
Fessenden, R. W., 185
Fessler, W. A., 613
Fetzer, U., 778
Feuer, B. I., 467
Feuer, H., 334, 683, 898
Field, L., 821
Fields, D. B., 611
Fields, D. L., 334
Fields, E. K., 466, 494, 627, 722
Fierz, H. E., 383
Fieser, L. F., 410, 852
Fieser, M., 852
Fife, W. K., 832
Figge, K., 365
Filler, 619, 863
Finckenor, L., 611
Finger, G. C., 504
Finkbeiner, H. L., 815
Finlayson, A. J., 269
Finley, K. T., 904
Finnegan, R. A., 429, 469, 476, 768
Finzi, P. V., 886
Firestone, R. A., 831
Firth, W. C., 559
Fisch, M., 793
Fischer, A., 119, 222
Fischer, E. O., 43, 66
Fischer, G., 93
Fischer, H., 66, 636
Fischer, H. P., 776, 777, 822
Fischer, M., 894
Fischer, M. S., 108
Fischer-Hjalmars, I., 33
Fish, A., 790, 793
Fishel, D. L., 675, 876
Fisher, I. P., 493
Fisher, T. H., 526
Fishman, D. H., 509
Fishman, J., 557
Fitzpatrick, J. D., 50, 51
Fitzsimmons, B. W., 38
Flautt, T. J., 469
Fleckenstein, L. J., 789
Fletcher, R. S., 234
Flood, S. H., 381, 382, 398, 407, 415
Flynn, E. W., 812
Flynn, J., Jr., 279
Flynn, R., 507
Fodor, G., 235

Foldi, V. S., 718
Folkers, K., 820
Fonken, G. J., 838
Fono, A., 545, 587, 825
Foote, C. S., 193, 622
Foote, J. L., 400
Forbes, E. J., 660
Ford, J. A., Jr., 707, 870
Forrest, J., 507, 508
Forrester, J. L., 611
Forsén, S., 194
Fort, A. W., 806, 807
Fort, R. C., Jr., 20, 129, 138, 258
Fossel, E. T., 843
Foster, D. J., 468
Foster, G., 538, 877, 880
Foster, R., 489
Foster, W. E., 608
Föttinger, W., 875
Fowler, R. G., 180
Fox, A. S., 538
Fox, I., 35, 244
Fox, R. C., 120
Fraenkel, G., 149, 221, 677
Fraenkel, G. K., 196
Frajerman, C., 650
Frampton, V. L., 49, 121
Francis, A. W., 408, 565
Francis, P. S., 864
Franconi, C., 221
Frank, C. E., 543, 608
Frank, G. A., 707
Franke, W., 760
Frankel, M. B., 334
Franklin, N. C., 192
Franzen, V., 163, 164, 406, 645, 764
Franzus, B., 642
Fraser, R. R., 300
Fray, G. I., 630
Frazier, H. W., 701
Fredenhagen, H., 909
Fredga, A., 85
Freedman, H. H., 49, 51
Freeman, J. P., 350
Freeman, P. K., 571
Freeman, R. C., 344, 591
Freeman, W. R., 533
Freenor, F. J., 345
Freidlina, R. K., 790, 792
Freifelder, M., 683
Frenkiel, L., 122
Frese, E., 722
Frey, A. J., 423
Frey, E. J., 601
Frey, H. M., 161, 164, 468, 643, 645, 646, 841
Fricke, H., 647
Fried, J. H., 574
Friedlin, L. Kh., 683
Friedman, B. S., 406
Friedman, J. P., 426
Friedman, L., 165, 411, 466, 494, 766, 876
Friedman, N., 127
Friedman, O. M., 676
Friedrich, E. C., 137
Friess, S. L., 205, 207
Frisch, H. L., 81
Frisch, M. A., 105
Frisell, C., 472
Fritsch, P., 812
Fritz, H. P., 43, 66, 67
Froemsdorf, D. H., 741, 746, 751, 764
Fröhlich, H., 813
Frommeld, H. D., 695, 901
Frost, A. A., 202, 208, 212
Fruit, R. E., Jr., 128
Fry, A., 271, 801, 802
Fuchs, H., 76
Fudim, M., 438
Fujimoto, H., 728, 837
Fujita, I., 93
Fukawa, H., 91
Fukuda, Y., 91
Fukui, K., 565, 728, 837, 839
Fukumoto, T., 372, 373, 907
Fukunaga, T., 895
Fuller, G., 611
Fulmer, R. W., 861
Funakubo, E., 645
Fung, D. P. C., 752
Furst, A., 593, 897, 908
Furukawa, J., 648
Furukawa, N., 500
Fuson, N., 180
Fuson, R. C., 424, 605
Fyfe, C. A., 489

Gable, C. M., 70
Gagnaire, D., 187
Gajek, K., 835
Gale, L. H., 106
Gall, J. S., 259, 288
Gallagher, W. P., 244
Galli, R., 400, 614, 623
Gams, A., 422
Gancher, E., 871
Ganellin, C. R., 80
Gannon, W. F., 811
Ganushchak, N. I., 615
Gaoni, Y., 52–55, 194
Garbisch, E. W., Jr., 459, 489, 498, 623, 736
Garcia, H., 405
Gardikes, J. J., 623
Gardner, I. J., 342
Gardner, P. D., 122
Garg, C. P., 600, 684

Garner, A. Y., 646
Garner, B. J., 882
Garner, C. S., 443
Garnett, J. L., 187
Garratt, P. J., 54
Garst, J. F., 551
Garst, R. H., 490
Gash, V. W., 861
Gaspar, P. P., 158, 160, 454
Gassman, P. G., 119, 138, 483
Gaston, L. K., 904
Gati, A., 642
Gaugler, R. W., 221
Gault, Y., 93
Gaverdovskaya, M., 862
Gavrilenko, V. V., 352, 684
Gayler, J. A., 423
Gaylord, G., 356
Gaylord, N. G., 348, 593, 678, 857, 894
Gazith, M., 342
Geels, E. J., 907
Geer, R. P., 751
Geibel, K., 360
Geissman, T. A., 908
Gelas, J., 667
Geller, B. A., 430
Geller, L. E., 850
Gellert, H. G., 767
Gembitskii, P. A., 387
Genaux, C. T., 838
Generosa, J. I., 160
Geneste, J., 613
Gent, B. B., 740
Geoghegan, P., Jr., 582
George, R. S., 686
Génard, L., 784
Gerecs, A., 428
German, L. S., 614
Gero, A., 60
Gerrard, W., 218, 757
Gershtein, N. A., 439
Gersmann, H. R., 464, 545
Gettler, J. D., 695
Ghatak, U. R., 896
Ghirardelli, R. G., 736
Ghosez, L., 625
Gibbons, W. A., 159
Gibbs, D. E., 323
Gibson, D. H., 837
Giddings, B., 534
Gielen, M., 451, 452
Gil-Av, E., 93, 838
Gilbert, A., 637
Gilbert, E. E., 330, 401, 402, 439, 462, 500, 546, 588, 677, 885
Gilchrist, M., 275
Gilde, H., 559
Gillam, A. E., 168, 173
Gillespie, R. J., 13, 100, 182, 217, 396, 398
Gilman, H., 468, 473, 476, 493
Gilmer, J. C., 469
Gilmore, W. F., 804, 807
Ginsburg, D., 37, 534, 538, 604, 612
Giovine, A., 887
Girard, C., 832
Giumanini, A. G., 358
Glasson, W. A., 289
Glaze, W. H., 767
Gleicher, G. L., 33, 49
Gleiter, R., 416
Glick, R., 266
Glick, R. E., 35, 244
Glockner, P., 642
Godfrey, T. S., 547
Goering, H. L., 148, 259, 267, 270, 546, 570, 571, 579, 832
Goetschel, C. T., 790, 862
Goetz, E., 576
Goggin, P., 426
Gold, H., 306
Gold, V., 125, 207, 228, 309, 382, 402, 453, 469, 489
Golden, D. M., 155, 455, 571
Golden, J. T., 430
Gol'dfarb, Ya. L., 119, 120, 234, 557
Goldfinger, P., 534, 536
Goldhamer, D., 117, 636
Goldhamer, D. L., 569
Goldmacher, J. E., 819
Goldman, G., 403, 413
Goldman, G. K., 58
Goldman, L., 882
Goldman, N., 360
Goldstein, E. J., 162
Goldstein, J. P., 646
Goldwhite, H., 574
Gollis, M. H., 334
Golubkin, L. N., 386
Gompper, R., 300
Goode, E. V., 19
Goodlett, V. W., 637, 638
Goodwin, T. H., 28, 117
Goosen, A., 850
Goralski, C. T., 400
Gordon, A. J., 579
Gordon, J. E., 64
Gordon, M., 45, 543
Gordy, W., 182, 195
Gore, P. H., 413, 415, 851
Gore, R. C., 175
Gorin, Yu. A., 583
Görler, K., 273
Gormisch, J. F., 400
Gorn, I. K., 583
Gosselain, P. A., 536
Gosser, L., 448

Göthlich, L., 657
Goto, R., 440
Gott, P. G., 637
Gould, D., 611
Gould, F. E., 777
Gover, T. A., 533
Govindachari, T. R., 422
Gower, L. H., 323
Grachev, M. A., 616
Gracheva, E. P., 569, 587
Graf, F., 326
Gragerov, I. P., 885
Graham, J., 398
Graham, J. D., 786
Grandberg, I. I., 776
Grandberg, K. I., 426
Granger, M. R., 222
Granito, C., 371
Grashey, R., 624, 626, 636, 643
Grasselli, P., 894
Graybill, B. M., 404
Grayson, M., 411
Greasley, P. M., 379
Green, B., 896
Green, J., 833
Green, J. H. S., 750
Green, M., 254, 289
Green, M. L. H., 66
Green, S. E. I., 151
Greene, F. D., 326, 561, 733
Greene, R. N., 832
Greenlee, K. W., 117
Greenwald, R., 703
Greenwood, F. L., 873, 874
Greenwood, H. H., 55
Gregoriou, G., 686
Greizerstein, W., 498
Gribchenko, E. A., 513
Griesbaum, K., 578, 588
Griffin, C. E., 708
Grigor, B. A., 222
Grigor'eva, N. Ya., 728
Grigoryan, A. A., 760
Grim, S. O., 704
Grimme, W., 121, 842, 843
Grimmelikhuysen, J. C., 873
Grisdale, P. J., 19
Grivas, J. C., 673
Grob, C. A., 529, 733, 772–774, 776, 777, 794, 822
Groenewege, M. P., 221
Grönwall, S., 472
Grosjean, M., 114
Gross, H., 419
Grovenstein, E., Jr., 405, 637, 798
Groves, L. G., 57
Groves, P. T., 225, 549
Grubbs, E. J., 811
Gruen, L. C., 694
Grundmann, C., 592, 720, 901
Grundon, M. F., 776, 893
Grunwald, E., 64, 208, 295, 296
Gudkova, I. P., 93
Guertin, D. L., 886
Guggenberger, L. J., 150
Guinn, V. P., 791
Gumby, W. L., 146, 289
Gundermann, K. D., 266
Gunstone, F. D., 616
Günther, H., 494
Günzl, W., 630
Gurien, H., 772
Gur'yanova, T. P., 473
Gusar', N. I., 899
Gutowsky, H. S., 182, 193, 504
Gutsche, C. D., 721, 780, 810, 811
Guzik, H., 557
Gwinn, W. D., 109, 139
Gwynn, D., 832

Haaf, W., 715
Haag, W., 769
Haag, W. O., 526, 751, 755, 792
Haake, P., 477
Haberfield, P., 300, 405, 448
Haberland, H., 408
Habich, A., 832
Habisch, D., 164
Hackett, M. C., 833
Häflinger, O., 20, 222
Hafner, H., 390
Hafner, K., 37, 41, 45
Häfner, K. H., 41
Hafner, W., 884
Hageman, H. A., 346
Hahn, C. S., 851
Hahn, W., 408
Halcour, K., 910, 911
Halek, G. W., 649
Hales, J. L., 421
Halevi, E. A., 215, 216, 486
Hall, D. N., 578
Hall, G. E., 396
Hall, H. K., Jr., 230
Hall, L. D., 105
Hall, L. H., 635
Hall, N. D., 312
Hall, W. L., 746, 748
Haller, I., 119
Hamblin, M. C., 412
Hambling, J. K., 531
Hamelin, R., 149, 686
Hamer, J., 504
Hamilton, G. A., 426
Hamlin, K. E., 483

Hammar, W. J., 582
Hammett, L. P., 129, 225, 312, 695
Hammond, G. S., 119, 160, 161, 390, 566, 751, 829, 837
Hammond, W. B., 806
Hammons, J. H., 137, 142, 218, 222
Hampton, K. G., 299, 507
Hamrick, P. J., Jr., 299, 357, 697
Han, Y. W., 434
Hanack, M., 101, 106, 109, 273
Hancock, C. K., 682
Hancock, J. W., 278
Hand, E. S., 276
Handler, G. S., 151
Hanford, W. E., 636, 766
Hannan, R. B., 409
Hansch, C., 862
Hansen, B., 703
Hansen, H., 830
Hansen, J., 510
Hansen, R. L., 451
Hanson, K. R., 84
Hantsche, H., 765
Hanzel, R. S., 557
Harada, R., 192
Harder, R. J., 158
Harder, U., 319
Hardie, B. A., 381, 382, 415
Härle, H., 628
Harris, B. W., 607
Harris, E. E., 147
Harris, J. F., Jr., 570, 580, 588, 613, 622, 665, 835
Harris, R. K., 192
Harris, T. M., 299, 369, 507
Harrison, A. C., 632
Hart, C. R., 451
Hart, H., 269, 411, 426, 432
Hartenstein, J., 119
Hartenstein, J. H., 843
Hartford, W. H., 880
Hartman, S., 216
Hartmann, V., 458
Hartter, D. R., 225
Hartung, W. H., 349
Harvey, D. R., 404
Harvey, G. R., 637
Harvey, M. C., 611
Harvey, R. G., 902
Harvey, S. H., 255
Harwood, H. J., 460
Hasek, R. H., 637, 667
Hasek, W. R., 677
Hasimoto, T., 689
Haske, B. J., 874
Haskelberg, L., 888
Hass, H. B., 527
Hassall, C. H., 823
Hassanali, A., 817
Hassel, O., 69, 104–106
Hassner, A., 777
Haszeldine, R. N., 427, 506, 632
Hatch, L. F., 284
Hatch, M. J., 815
Hatz, E., 324
Haubenstock, H., 681
Hauck, F., 447
Hauptmann, H., 556
Hauptmann, S., 867
Hause, N. L., 729, 731
Hauser, C. F., 357
Hauser, C. R., 299, 357, 365, 366, 369, 507, 517, 518, 658, 685, 696, 697, 736, 776, 783, 827, 888
Häuser, H., 159
Hausser, J. W., 286
Haven, A. C., 842
Hawthorne, J. O., 435
Hawthorne, M. F., 390, 659
Hay, A. S., 861
Hayashi, M., 260
Hayes, S., 149
Haynes, N. B., 884
Hazdra, J. J., 598
Head, A. J., 748
Heaney, H., 476, 492, 502
Heath, N. S., 770
Hecht, R., 792
Heck, R., 259, 266, 267
Hedaya, E., 536
Hedberg, K., 51
Hedberg, L., 51
Heeren, J. K., 703, 704
Hegenberg, P., 55
Heiba, E. I., 526, 792
Heilbron, I., 913
Heim, P., 895
Hein, G. E., 486
Heindel, N. D., 787
Heine, R. F., 279, 569
Heinemann, G., 216
Heischkeil, R., 317, 811
Heiszwolf, G. J., 307
Heitmann, P., 502
Hekkert, G. L., 75
Heldt, W. Z., 386, 821, 822
Helgren, P. F., 339
Heller, C. A., Jr., 540
Hellman, H. M., 572
Hellmann, H., 670
Helmer, F., 510
Helmkamp, G. K., 770
Hems, M. A., 637
Henbest, H. B., 578, 866, 893
Henderson, L. J., 187
Henderson, R. B., 302, 345
Henderson, W. A., Jr., 332, 646

Hendley, E. C., 851
Hendrickson, J. B., 514
Hendriks, H., 412
Hendry, D. G., 532
Hendy, B. N., 305
Henecka, H., 575
Henkler, H., 876
Henley, M. B., 750
Henne, A. L., 342, 533
Henry, J. P., 606, 837
Henry, P. M., 884
Hepp, H. J., 601, 607
Heppolette, R. L., 216
Hérbert, N. C., 474
Herbert, W., 353
Herd, A. K., 338
Hergenrother, W. L., 882
Herk, L., 575
Herling, J., 838
Hermánek, S., 21
Herndon, W. C., 269, 635, 750
Herrick, E. C., 645, 904
Hershenson, H. M., 173, 180
Hershkowitz, R. L., 344
Hertler, W. R., 158
Herweh, J. E., 374
Herynk, J., 559
Herz, A. H., 385
Herzberg, G., 155, 161
Heslop, R. B., 427
Hess, G. P., 337
Hess, R. E., 636, 723
Heunisch, M., 765
Heusler, K., 532, 542, 793
Hey, D. H., 529, 530, 551, 570, 607, 913
Heydkamp, W. R., 591
Heyer, E. W., 832
Heyman, D., 451
Heyns, K., 862
Heywood, D. L., 865
Hiatt, R. R., 215
Hibbert, P. G., 529
Hickinbottom, W. J., 349, 411, 429, 877
Higasi, K., 3, 30
Higginbotham, H. K., 23, 24
Higuchi, T., 338
Hilbert, P., 644
Hill, A. S., 351
Hill, D. G., 369
Hill, H. A. O., 504, 507
Hill, J. A., 452
Hill, K. R., 614
Hill, R., 50
Hill, R. K., 603, 628, 776, 777, 822, 826, 833
Hiller, G., 665, 894
Hiller, J. J., Jr., 400
Himoe, A., 58, 387
Hine, J., 59, 158, 163, 166, 240, 304, 420, 466, 479, 598, 643, 736
Hinman, R. L., 191, 536, 614
Hino, J. B., 535
Hinze, J., 18
Hirschberg, Y., 641
Hirst, D. M., 17, 28
Hirst, J., 498
Hishida, S., 278
Hite, G., 808
Hock, H., 543
Hodge, J. D., 127, 128
Hodgson, H. H., 484
Hodnett, E. M., 738
Hoegerle, R. M., 774, 794
Hoelscher, H. E., 595
Hofeditz, W., 153
Hoffman, D. M., 620
Hoffman, R. A., 550
Hoffmann, A. K., 145
Hoffmann, F. W., 557
Hoffmann, H., 440, 705
Hoffmann, H. M. R., 255, 750
Hoffmann, R., 633, 635, 837, 839
Hoffmann, R. W., 159, 494
Hofman, H. J., 402
Hofman, P. S., 433
Hofmann, A. W., 760
Hofmann, J. E., 421, 509, 764
Höft, E., 419
Hogben, M. G., 119
Hogen-Esch, T. E., 147
Höger, E., 869
Hogeveen, H., 583
Hojo, M., 259, 436
Holiday, E. R., 289
Holl, R., 903
Holleman, A. F., 388
Hollingsworth, C. A., 151
Holloway, F., 863
Hollowell, C. D., 23
Hollyhead, W. B., 495
Holmberg, B., 310
Holme, D., 594
Holmes, H. L., 167, 357, 626
Holmes, J., 827
Holmes, R. R., 244, 884
Holness, N. J., 108, 137, 738, 786
Holt, P. F., 505
Holtz, H. D., 20, 286
Holý, A., 418
Homberg, O., 608
Homer, R. B., 313
Hontschik, I., 424
Hood, F. P., 105, 192
Hoogzand, C., 123
Hooton, S., 593, 897
Hoover, F. W., 591
Hooz, J., 469
Hopff, H., 642
Hopperdietzel, S., 612

Hopton, J. D., 17
Horeau, A., 91
Horiuti, I., 595
Hörmann, H., 678
Horner, L., 76, 162, 440, 535, 705, 810, 902
Hörner, L., 588
Horning, E. C., 883
Horning, W. C., 402
Hornke, I., 813
Horrom, B. W., 289
Hotta, H., 539
Houbiers, J. P. M., 75
House, H. O., 357, 359, 362, 458, 463, 464, 592, 597, 604, 605, 618, 670, 702, 707, 771, 804, 807, 811, 816, 823, 857, 890, 898
House, W. T., 861
Houser, J. J., 127, 128, 736
Houston, D., 137
Höver, H., 49
Howe, C. A., 530, 552
Howe, R., 136, 137
Howell, C. F., 762
Howell, R. G., 611
Howells, W. G., 550
Howlett, K. E., 751
Hoye, P. A. T., 255
Hrutfiord, B. F., 483, 502, 507
Hsu, J., 151
Hsu, S. K., 446
Huba, F., 498
Hübel, W., 123
Huber, G., 869
Huber, J. E., 267
Huber, M. B., 605
Huber-Buser, E., 120
Huber-Emden, H., 333
Hubert, A. J., 454, 767
Hückel, W., 131
Hudson, B. E., Jr., 366
Hudson, R. F., 254, 289, 308
Hudec, J., 609, 628
Hudson, B. E., Jr., 588
Huebner, C. F., 638
Huet, J., 690
Hughes, E. D., 233, 252, 255–257, 287, 312, 398, 429, 430, 444–446, 451, 485, 519, 547, 548, 731, 734, 740, 741, 744, 746, 747, 783, 828, 830
Hughes, W. B., 703, 704
Hughmark, P. B., 821
Huisgen, R., 488, 492, 493, 499, 502, 504, 624–626, 636, 643, 818, 900
Huisman, H. O., 533
Huitric, A. C., 192
Humffray, A. A., 240
Humphlett, W. J., 685
Humphrey, J. S., Jr., 216
Hung, N. M., 582
Hunger, A., 481
Hünig, S., 482, 593, 596
Hunsberger, I. M., 55, 882
Hunt, J. H., 675
Hunter, D. H., 147
Hunter, L., 64
Huntress, E. H., 942
Hurd, D. T., 148, 442, 470, 583
Hurst, J. J., 99
Hurwitz, M. J., 790
Husk, G. R., 650
Hutchison, C. A., 159
Hutchison, J. D., 288
Huybrechts, G., 534
Huyffer, P. S., 165
Huyser, E. S., 533–535, 570, 606, 615
Hymers, W. A., 492
Hyne, J. B., 293

Ibbitson, D. A., 19
Ibne-Rasa, K. M., 436, 516
Ichikawa, K., 679, 681
Iczkowski, R. P., 18
Ide, W. S., 714
Iffland, D. C., 300, 484
Ikegami, S., 582
Ikenberry, E. A., 814
Iliceto, A., 261, 373
Imaida, M., 91
Imamura, S., 609
Impastato, F. J., 483
Inamoto, N., 191
Indzhikyan, M. G., 760
Ingberman, A. K., 554
Ingham, R. K., 559
Ingold, C. K., 84, 242, 252, 255–257, 281, 287, 295, 310, 311, 312, 398, 429, 442, 444–446, 451, 457, 485, 519, 547, 548, 731, 734, 740, 741, 744, 746, 747, 828, 830
Ingold, E. H., 310
Inman, C. E., 458
Inoue, T., 538
Insole, J. M., 491
Inukai, T., 236, 240
Ioffe, B. V., 408
Ioffe, D. V., 886
Ioffe, S. L., 683, 897
Irelan, J. R. S., 904
Irsa, P., 594
Isaacs, N. S., 302
Isaev, I. S., 439
Isaguliants, G. V., 755
Ishak, M. S., 812, 908
Ishii, Y., 690
Israelstam, S. S., 487
Ito, A., 532
Ito, M., 55
Ito, R., 530
Ito, Y., 726

Itoh, K., 160
Iurkevich, A. M., 615
Izsak, D., 104
Izumi, Y., 91
Izzo, P. T., 363

Jackman, L. M., 52, 55, 182, 189, 192, 194, 593, 857, 861
Jacknow, B. B., 534
Jackson, E. L., 868
Jackson, R. A., 774
Jacobs, T. L., 284, 361, 455, 578, 765
Jacobson, H. I., 902
Jacobson, R. R., 832
Jacox, M. E., 159, 645
Jaffé, H. H., 18, 168, 173, 239, 240, 387, 851
Jagow, R. H., 216
Jakobsen, H. J., 472
Jambotkar, D., 707
James, E. L., 396
James, J. C., 334
Janda, H., 685
Janiak, P. St., 148
Jann, K., 723
Jaques, D., 306, 307
Jaruzelski, J. J., 225
Jarvie, A. W. P., 402
Jaunin, R., 903
Jayaraman, H., 276
Jeffery, E. A., 323, 425
Jeffrey, J. C., 285
Jeger, O., 797
Jen, M., 23
Jencks, W. P., 238, 275, 276, 490, 651, 658
Jenner, E. L., 603
Jenny, E. F., 492, 826
Jenny, F. A., 733
Jensen, E. V., 902
Jensen, F. R., 105, 106, 138, 192, 403, 413, 444, 451, 778
Jensen, W. N., 656
Jentzsch, J., 549, 665, 894
Jeremić, D., 542
Jerosch Herold, B., 158
Jeskey, H., 421
Jewett, J. G., 216, 268
Jira, R., 884
Johnson, A. P., 882
Johnson, A. W., 704
Johnson, C. R., 254
Johnson, D., 559
Johnson, D. L., 334
Johnson, F., 344
Johnson, G. H., 276
Johnson, G. S., 777
Johnson, H. W., Jr., 80, 886
Johnson, J. R., 636, 698, 723
Johnson, M. D., 240
Johnson, R. G., 559
Johnson, R. N., 578
Johnson, S. L., 276
Johnson, T. A., 832
Johnson, W. S., 105, 192, 317, 414, 696
Johnston, K. M., 549
Johnstone, R. A. W., 626, 764, 825, 836
Jonassen, H. B., 610
Jones, D. A. K., 750
Jones, D. M., 307
Jones, D. N., 749
Jones, D. W., 50, 544
Jones, E. R. H., 83, 590, 594
Jones, F. N., 518
Jones, G., 512, 697, 820
Jones, G. C., 517
Jones, J. I., 421
Jones, J. M., 215, 335
Jones, L. C., 173
Jones, M., 835
Jones, M., Jr., 164, 843
Jones, N., 616
Jones, P. R., 62
Jones, R. A. Y., 189, 221
Jones, R. G., 468, 473, 476
Jones, R. N., 175, 181
Jones, V. K., 707
Jones, W. H., 627, 675
Jones, W. J., 882
Jones, W. M., 644, 813
Jönsson, P., 472
Jorgenson, M. J., 225, 593
Josey, A. D., 709
Juan, C., 193
Julia, M., 532
Juliusburger, F., 255
Jullien, J., 576
Jungk, H., 411, 433
Jurewicz, A. T., 411
Jurgeleit, W., 902
Juvet, R. S., Jr., 662

Kaandrop, A. W., 402
Kabasakalian, P., 851
Kader, A. T., 280
Kadin, S. B., 593
Kaeding, W. W., 511, 546, 877
Kaffenberger, T., 774
Kahn, G. M., 660
Kahr, K., 884
Kaiser, E. M., 598, 599
Kaiser, E. T., 148
Kajimoto, Y., 560
Kalvoda, J., 532, 542, 793
Kamał, A., 666

Kamernitskii, A. V., 651
Kamlet, M. J., 878
Kammann, K. P., Jr., 363
Kampmeier, J. A., 751
Kan, R. O., 416
Kanner, B., 228
Kantor, S. W., 518, 783, 827, 888
Kaplan, E. P., 363
Kaplan, F., 192, 475
Kaplan, L., 119, 652
Kaplan, L. A., 897
Kaplan, M. L., 64, 295
Kaplan, R. B., 341
Karabatsos, G. J., 187, 193, 440, 786, 789
Kara-Murza, C. G., 616
Kariv, E., 893
Karkowski, F. M., 12
Karl, R., 549
Karle, I. L., 198
Karle, J., 198
Karplus, M., 193
Kasai, P. H., 23
Kasturi, T. R., 896
Kato, T., 507
Katritzky, A. R., 61, 182, 189, 221, 225
Katz, T. J., 46, 54, 631
Kauffmann, T., 494, 510, 876
Kaufman, P. R., 459
Kauzmann, W., 86
Kawabata, N., 648
Kawakami, J. H., 582
Kawamura, S., 901
Kawanishi, M., 500
Kawano, K. I., 159
Kawasaki, A., 667
Kaya, K., 171
Kazan, J., 326
Kazanskii, B. A., 645
Keaton, O. D., 675
Keaveney, W. P., 871
Keefer, R. M., 66, 261, 440
Keller, H., 67, 80
Keller, R. N., 400
Kellogg, R. E., 58
Kellom, D. B., 748
Kelly, C. A., 637
Kemp, R. T., 737
Kende, A. S., 804
Kennedy, J., 807
Kenner, G. W., 505
Kent, B. A., 520
Kenyon, J., 254, 312, 783
Kergomard, A., 613
Kerlinger, H. O., 546
Kern, F., 838
Kerr, J. A., 24
Kershner, L., 276
Kessler, H., 647
Kester, F. L., 25
Ketcham, R., 707
Ketley, A. D., 317
Kevill, D. N., 276
Khalaf, A. A., 410
Kharasch, M. S., 149, 353, 354, 471, 531, 545, 549, 555, 573, 587, 684, 825
Khorana, H. G., 321
Khorlina, I. M., 352
Khorlina, M. Ya., 790, 792
Kibler, L. M., 536
Kice, J. L., 330
Kiedaisch, W., 647
Kienitz, H., 436
Kiertead, R. W., 423
Kiess, A. A., 872
Kiji, J., 609, 616
Kilpatrick, J. E., 109
Kilpatrick, M., 380
Kim, H., 139
Kim, J., 443, 451
Kimura, K., 159, 171
Kindler, K., 900
King, J. A., 910
King, J. F., 95, 770, 795
King, R. B., 44
King, R. W., 747, 751, 756
Kingsbury, C. A., 448, 764
Kintner, R. R., 848
Kirby, A. J., 490
Kiritani, R., 372, 373, 500, 501
Kirmse, W., 158, 163, 165, 166, 466, 643, 722, 810
Kirn, W. N., 677
Kirrman, A., 149
Kirsanov, A. V., 338, 677
Kise, M., 500
Kise, M. A., 613
Kish, F. A., 567
Kiss, J., 235
Kissel, W. J., 879
Kitahara, Y., 639
Kitahonoki, K., 899
Kitching, W., 143, 222
Klaeboe, P., 69
Klages, F., 676
Klamann, D., 327, 374
Klasinc, L., 737
Klass, D. L., 656
Klebe, J., 162, 646
Kleeman, M., 637
Klein, E., 113
Klein, H. S., 21
Klein, J., 605
Klein, O., 657
Kleinberg, J., 534, 857
Kleiner, H., 159
Kleinschmidt, R. F., 590

Klimisch, R. L., 742
Kline, M. W., 826
Klinedinst, P. E., Jr., 259
Klingensmith, G. B., 438
Kloetzel, M. C., 626
Kloosterziel, H., 644
Klosa, J., 338
Kluge, M., 867
Klumpp, G., 843
Klusacek, H., 843
Klyne, W., 84, 104, 109, 110, 112, 113
Knauss, E., 627, 628
Knight, J. C., 896
Knoeber, M. C., 12
Knotnerus, J., 578
Knowles, J. R., 395, 498
Knox, B. E., 24, 25
Knox, G. R., 762, 893
Knox, L. H., 43, 164, 258, 466, 647, 783
Knunyants, I. L., 614
Knupfer, H., 778
Knutson, D., 206
Köbrich, G., 442, 494, 728, 755, 765, 774, 812, 813
Kobrina, L.S., 498
Kobsa, H., 429
Koch, F. W., Jr., 412
Koch, W., 382
Kochetkov, N. K., 616
Kochi, J. K., 404, 546, 559, 587, 713, 878
Koda, S., 676
Koenig, P. E., 335
Koenig, T., 536
Kofron, W. G., 299
Kogan, G. A., 33
Kohl, D. A., 23
Kohnstam, G., 259, 261, 296
Kokes, R. J., 596
Kolinskii, R., 122
Kolos, W., 7
Kolthoff, I. M., 218, 222
Kolyaskina, Z. N., 615
Kompa, K., 400
Koncos, R., 406, 466
Kondrat'eva, L. V., 569, 590
Kondratieva, G. V., 871
König, C., 41
König, H., 502
König, J., 842
Konovalov, A. I., 632
Kooyman, E. C., 39, 405, 412, 439, 533, 750, 751
Kopecky, K. R., 90, 161, 447
Kopp, J., 215
Koptyug, V. A., 439
Koreshkov, Yu. D., 49, 646
Kornblum, N., 300, 301, 341, 484, 514, 547, 659, 882, 885
Kornegay, R. L., 105, 135, 192
Korte, S., 121
Kortüm, G., 221
Korytnyk, W., 680, 895
Kosak, J. R., 432
Kosel, C., 510, 876
Kosicki, G. W., 457
Koski, W. S., 153
Koskikallio, 226
Kosower, E. M., 66, 154, 297, 459, 529
Kost, V. N., 790, 792
Kotera, K., 899
Koubek, E., 516
Kovachic, D., 578
Kovacic, P., 400, 401, 405, 412, 426, 546
Kovacs, J., 269
Kovalev, B. G., 707
Koyama, K., 425
Kozlov, V. V., 399, 484, 503, 514, 553
Kraft, L., 868
Krapcho, A. P., 165, 673, 785
Krasna, A. I., 596
Krasnaya, Zh. A., 714
Krasnobajew, V., 774
Kratzer, O., 704, 707
Krauch, H., 43
Kraus, K. W., 362, 691
Krebs, A., 49, 806
Krebs, W., 49
Kreespan, C. G., 611
Kreevoy, M. M., 451
Kresge, A. J., 252, 382
Kreuder, M., 41
Krieger, K. A., 681
Krieger, M., 525
Krimm, H., 422
Kristiansen, O., 807
Kritchevsky, J., 573
Kriz, G. S., Jr., 216
Kříž, J., 361
Krizhechkovskaya, N. I., 403
Kröhnke, F., 697
Kromhout, R. A., 64
Kropf, H., 543
Kruck, P., 869
Krüerke, U., 123
Kruger, J. E., 268, 786
Krupicka, J., 760, 864
Krupin, B. S., 583
Kruse, C. W., 590
Kruse, R. B., 569
Kubo, M., 44
Kuchar, E. J., 611
Kucherov, V. F., 110, 707, 714, 728
Kuchitsu, K., 23
Kudryavtsev, R. V., 851
Kudryavtsev, Yu. P., 52
Kuffner, F., 689
Kühle, E., 910

Kuhn, D. A., 237
Kuhn, H., 172
Kuhn, S. J., 129, 379, 381, 382, 396, 397, 398, 406, 407, 415, 416, 418, 463
Kuivila, H. G., 348, 351, 505, 681
Kujanpåå, T., 716
Kuksis, A., 687
Kul'bovskaya, N. K., 569, 587
Kulka, M., 423
Kullnig, R. K., 192
Kumli, K. F., 705
Kundiger, D. G., 814
Küng, W., 121, 789
Kuo, C. H., 429
Kupchan, S. M., 278
Kurabayashi, K., 843
Kurkjy, R. P., 319
Kursanov, D. N., 44, 49, 646, 855
Kurz, M., 404
Kurz, M. E., 426, 546
Kutta, H. W., 768
Kwan, T., 93
Kwart, H., 20, 460, 620,732, 833, 864, 870
Kwei, G. H., 23
Kwiatkowski, G. T., 139, 267
Kwie, W. W. L., 874
Kyriakis, A., 412

Laba, V. I., 569, 587
Labib, A., 428
Lacey, R. N., 315, 585, 723
Lachmann, B., 159
Lack, R. E., 579
LaCount, R. B., 704
Ladbury, J. W., 857
Ladenheim, H., 314
LaFlamme, P. M., 644
Laidler, K. J., 26
Lakritz, J., 818
LaLancette, E. A., 54
Lambert, J. B., 108, 843
Lambert, J. L., 146
Lambert, R. W., 382
Lampman, G. M., 119, 354
Landesman, H., 464
Landolt, R. G., 832
Landor, P. D., 272
Landor, S. R., 91, 272, 645, 833
Lane, J. F., 817
Lang, D., 630
Láng, L., 173
Lange, G., 149
Lange, R. M., 400, 412
Langemann, A., 447
Langlois, D. P., 292
Langworthy, W. C., 470
Lansbury, P. T., 600, 679, 821, 827
Lantz, R., 503
Lapierre, J. C., 411
Lapporte, S. J., 521
LaPrade, J. E., 648
Lapworth, A., 710
Larchar, A. W., 665
Larkworthy, L. F., 485
Larnaudie, M., 181
Larsen, D. W., 571
Larsen, E. H., 472
Larsen, J. W., 260
Laszlo, P., 193, 215
Latourette, H. K., 414
Lau, H. H., 101, 109, 561
Lauer, W. M., 832
Laughlin, R. G., 164
Laurie, V. W., 20
Lautenschlaeger, F., 106
Lauterbur, P. C., 182
Lavanish, J., 119
Lawesson, S., 472
Lawson, A., 55
Lawson, D. D., 40
Lawton, B. T., 851
Lawton, R. G., 267
Lazaris, A. Ya., 661
Lazdins, D., 430
Leake, P. H., 551
Leake, W. W., 506
Lease, M. F., 596
LeBel, N. A., 267, 712, 732, 760, 762
Le Bris, A., 669
L'Écuyer, P., 516
Lederer, M., 613
Ledger, R., 759
Lednicer, D., 80, 658
Ledwith, A., 164, 285, 721, 811
Lee, C. C., 41, 139, 268, 269, 412, 786
Lee, D. F., 328
Lee, D. G., 269, 864
Lee, K. W., 851
Lee, L., 573, 577
Lee, M. K. T., 65
Lee, W. G., 147
Leebrick, J. R., 608
Leermakers, P. A., 161
Lees, W. A., 64
Lefebvre, G., 669
Le Fèvre, R. J. W., 104
Leffek, K. T., 215, 216
Lefferts, E. B., 124, 686
Leffler, J. E., 125, 208
Leffler, M. T., 510
LeGoff, E., 45, 354, 648
Legrand, M., 114
Leimer, K. E., 741
Leinhard, G. E., 276
Leipert, R., 188

Leisten, J. A., 306, 307, 315
Leitch, L. C., 578
LeMahieu, R., 894
Le Maistre, J. W., 776
Lemal, D. M., 119, 159, 645
Lemieux, R. U., 192, 875
Lemke, T. L., 807
Lempert, K., 322
Lendle, W., 482
Le Noble, W. J., 139, 300, 304
LeNy, G., 267
Leo, A., 864
Leonard, N. J., 120, 300, 668, 723, 861
Leone, A., 712
Lepley, A. R., 68, 358, 502
Lepse, P. A., 540
Lesage, M., 141
Lethbridge, J. W., 427
Letsinger, R. L., 755
Leuschner, G., 549
Levasseur, L. A., 835
Levi, G. I., 26
Levina, R. Ya., 387
Levine, I. N., 23
Levine, R., 483, 506
Levisky, J. A., 400, 401
Levit, A. F., 885
Levitz, M., 254
Levy, A. J., 569
Levy, H., 834
Levy, J. F., 259
Levy, L. B., 551
Lewandowski, K. M., 267
Lewin, A. H., 508
Lewis, A., 187
Lewis, E. S., 205, 240, 269, 491
Lewis, G. N., 252
Lewis, I. C., 35, 243, 244
Lewis, R. N., 148, 442, 470, 583
Lewis, T. B., 352
Libby, E. M., 396
Liberman, A. L., 653
Lichtenberger, J., 585
Lide, D. R., Jr., 19, 23, 24, 102, 182
Lieb, J., 385
Liehr, A. D., 86
Lien, A. P., 433
Liesemer, R. N., 712
Lieske, C. N., 712
Light, R. J., 299
Lightner, D. A., 769
Lin, J., 767
Lincoln, D. N., 128
Lindsay, D. G., 466
Lindsay-Smith, J. R., 539
Lindsey, A. S., 421
Lindsey, R. V., Jr., 558, 574, 603
Linnett, J. W., 17, 28
Linstead, R. P., 673, 861
Lion, C., 650
Lipscomb, W. N., 51, 198
Liston, T. V., 469
Little, J. C., 632
Little, W. F., 43
Little, W. T., 699, 700
Littler, J. S., 855, 857, 865, 870
Liu, J. S., 128
Liu, L. H., 122
Livingston, R., 212
Llewellyn, J. A., 215, 216
Loan, L. D., 873
Lock, G., 654
Locke, D. M., 505
Loder, J. D., 83
Loeppky, R. N., 486
Loev, B., 310
Loewenstein, A., 221
Loftfield, R. B., 805
Logan, T. J., 469, 614, 815
Logullo, F. M., 494
Lokensgard, J. P., 119
Lombard, R., 617
Long, F. A., 65, 216, 224, 226, 312, 457, 662
Long, R. A. J., 524
Longuet-Higgins, H. C., 46, 48, 839
Lonsdale, K., 23
Looney, C. E., 194
Lopatin, B. V., 569
Lora-Tamayo, M., 628
Lorber, M. E., 688
Lorenc, Lj., 542
Lorenz, D. H., 440
Lorenz, O., 873
Lorette, N. B., 833
Lossing, F. P., 493
Loudon, J. D., 43, 498, 538
Louw, R., 439, 751
Lovald, R. A., 159
Lovering, E. G., 26
Lowe, G., 861
Lowe, J. P., 103, 742
Luborsky, F. E., 380
Lucas, G. B., 823
Lucas, H. J., 264, 477
Lugasch, M. N., 225
Lührs, K., 900
Lukasiewicz, A., 669
Lukaszewski, H., 676
Lukina, M. Yu., 117, 579
Lundeen, A. J., 754
Lüttringhaus, A., 906
Lutz, R. E., 737
Lutz, R. P., 187
Lux, R., 900
Lyle, G. G., 110
Lyle, R.E., 110
Lynch, J. F., 197
Lynn, K. R., 435

Ma, V., 325
Maahs, G., 55
Maas, L. W., 876
Maas, W., 658
McAllister, S. H., 866
McArole, J., 480
McBay, H. C., 549
McBee, E. T., 119, 403, 527, 627
McCain, M. E., 741, 746
McCants, D., 254
McCasland, G. E., 74
McCaulay, D. A., 433
Macchia, B., 308
Macchia, F., 308
McClellan, A. L., 19, 63
McClelland, B. J., 158
McClure, J. D., 823
Maccoll, A., 172, 211, 455, 728, 747, 750
McCollum, J. D., 43
McConnell, H. M., 155
McCorkindale, N. J., 807
McCormick, J. R. D., 704
McCoy, L. L., 535, 536, 649
McCrae, W., 549
McCullough, J. J., 578
McDaniel, D. H., 20, 65, 222
McDonald, R. N., 621
McElvain, S., 904
McEwen, W. E., 705, 857
McEwen, W. K., 222
McFarlin, R. F., 351
McGee, T. W., 611
McGlynn, S. P., 67
McGrath, B. P., 537
Mach, G. W., 225
Machleidt, H., 458
Maciel, G. E., 193
McIntyre, J. S., 126
McKee, D. W., 595
McKee, R. L., 427
McKeever, C. H., 424
McKellin, W. H., 901
McKelvie, N., 703
McKenna, J., 740, 759
McKenna, J. F., 690
McKenzie, A., 565
Mackenzie, K., 270, 453
McKervey, M. A., 120, 789
Macklen, E. D., 218
McKusick, B. C., 574, 638, 644, 665
McLafferty, F. W., 196, 197
McLeod, R. K., 666
McLeod, W. D., Jr., 691
McMahon, M. A., 410
McMahon, R. E., 324
McMillan, F. H., 910
McManimie, R. J., 279, 569
McMurray, W., 198
McNees, R. S., 469
McNelis, E., 436
McNesby, J. R., 540
MacNulty, B. J., 734, 746, 747
McOmie, J. F. W., 37, 45, 67, 344
MacPeek, D. L., 619
McPhail, A. T., 65
McQuillin, F. J., 592
McRowe, A. W., 137
McShane, H. F., Jr., 718
McSweeney, J. V., 509
McTigue, P. T., 222, 541, 694
McWeeney, R., 55
Maeda, S., 505
Maerker, A., 702
Magerlein, B. J., 701
Maggio, T. E., 775
Magi, M., 894
Magnetat, J., 903
Magnotta, F. A., 374
Magnusson, B., 665
Magoon, E. F., 791
Mahadevan, A. P., 484
Mahler, H. R., 215
Mahler, J., 66
Mahler, W., 158, 646
Maimind, V. I., 44, 851, 907
Mains, H. E., 546
Maitlis, P. M., 51
Mak, T. C. W., 51
Makarova, L. G., 513
Maki, A. H., 196
Makin, S. M., 605
Makisumi, Y., 833, 834
Makovetskii, K. L., 642
Maksimović, Z., 542
Malchick, S. P., 409
Mallan, J. M., 598
Mallet, A. I., 870
Mallory, H. E., 907
Mamalis, P., 833
Mamedova, Yu. G., 154
Mamuzic, R. I., 542
Manakov, M. N., 162
Mancuso, N. R., 821
Mandelcorn, L., 70
Manderola, O. B. de, 717
Mango, F. D., 793
Mangold, D., 525, 627
Manion, J. M., 750
Manly, T. D., 857
Mann, D. E., 19, 24, 159
Mann, F. G., 75
Mannhardt, H., 172
Manske, R. H. F., 423
Manson, D. L., 344
Mantecon, J., 477
Marais, D. J., 32
March, J., 477, 480, 686
Marchand, A. P., 19

Marcus, N. L., 850
Marcus, S. H., 65
Margolin, Z., 216
Margrave, J. L., 18, 105
Margulis, T. N., 108
Marica, E., 67
Marino, G., 391, 392
Marisco, W. E., 593
Mark, V., 272
Markby, R., 608
Märkl, G., 709
Marktscheffel, F., 350, 869
Marple, K. E., 866
Marquis, E. T., 122
Marr, E. B., 932, 953
Marsh, C. R., 495
Marshall, B., 880
Marshall, J. L., 138
Marshall, T. B., 636, 723
Marshall, W. S., 821
Martens, G., 534
Martin, B., 478
Martin, E. L., 893
Martin, G., 418
Martin, J. C., 526, 536, 637, 667
Martin, J. G., 628
Martin, J. M., Jr., 163
Martin, K. J., 350
Martin, M., 418
Martin, M. M., 120, 789, 792, 793
Martin, R. B., 312
Martin, W. B., 668
Martinek, T. W., 656
Martinelli, L., 707
Martin-Smith, M., 187
Martynov, V. F., 701
Marvel, C. S., 71, 73, 76
Marvell, E. N., 438, 832
Marxmeier, H., 876
Maryott, A. A., 19
Masamune, S., 119
Maskill, H., 292
Maslin, D. N., 352, 684
Mason, R., 55
Mason, S. F., 86, 168
Massad, M. K., 334
Masterman, S., 252, 255, 312, 744
Masuda, S., 191
Mataga, N., 160
Mateescu, G., 67
Mateos, J. L., 447
Matesich, M. A., 584
Mathew, K. K., 769
Matice, J. J., 429
Matlack, A. S., 595
Matlack, E. S., 454
Matouchová, L., 690
Matoush, W. R., 76
Matsen, F. A., 168
Matsui, H., 277
Matsukawa, Y., 899
Matteson, D. S., 450
Matthews, W. E., 423
Matveeva, M. K., 513
Matzner, M., 319
Maw, G. A., 744, 747
Maxwell, R. J., 788
Maya, W., 759
Mayahi, M. F., 339
Mayer, M., 807
Mayer, R., 665, 774, 894
Mayer, U., 122, 546
Mayer, W. J., 672
Mayo, F. R., 573, 580
Mayo, P. de, 781, 790, 795
Mazur, R. H., 139
Meakins, G. D., 620
Meckel, W., 843
Medvedova, A. A., 683
Meek, J. S., 729
Meerwein, H., 466, 514, 784
Mehmedbasiçh, E., 712
Mehta, A. S., 760
Meiboom, S., 221
Meier, G. F., 773
Meinwald, J., 99, 119, 187, 614
Meinwald, Y. C., 80, 614
Meisenheimer, J., 489
Meislich, H., 240
Meister, H., 760
Meisters, G., 459
Melander, L., 214, 378, 396, 514
Melby, L. R., 158, 574
Melera, A., 53
Mellon, M. G., 932, 953
Meloy, G. K., 192
Menapace, L. W., 348, 505
Menger, F., 119, 645
Mengler, H., 625
Merbach, A., 306
Meredith, C. C., 40
Merényi, R., 119, 123, 642, 842, 843
Merk, W., 360
Merker, R. L., 323
Merrall, G. T., 612
Merritt, R. F., 611, 612, 884
Merrow, R. T., 778
Merten, R., 590
Mertz, C., 764
Merz, E., 551
Merzoni, S., 650
Meskin, A. J., 751
Meyer, F. J., 149
Meyer, K. H., 60
Meyer, M. W., 383, 434, 439
Meyer, R. B., 299
Meyers, C. Y., 833
Meyerson, S., 43, 494, 551, 627, 786

Meyerson, S., 43, 494, 551, 627, 786
Mibae, J., 907
Michael, A., 565, 731
Michael, D., 440
Michailenko, I. E., 753
Michalski, J., 189
Michel, E., 503
Mićović, V. M., 679
Miekka, R. G., 736
Mielert, A., 630
Miginiac, P., 158
Migita, T., 530
Mihailović, M. Lj., 542, 679, 866
Mikeska, L. A., 712
Mikhailov, B. M., 33
Miki, T., 338
Miklukhin, G. P., 349, 682
Mikol, G. J., 369
Mikulak, R., 278
Miles, D. H., 55
Miles, J. H., 435, 869
Miles, M. L., 299, 369
Millar, I. T., 476, 512
Millar, R. W., 70
Millen, D. J., 103, 396, 398
Miller, A. E. G., 684
Miller, B., 300
Miller, B. J., 91
Miller, C. E., 596
Miller, E. B., 491
Miller, J., 224, 497, 686
Miller, R. E., 872
Miller, R. G., 494, 627
Miller, S. I., 65, 147, 575
Miller, V. B., 342
Miller, W. T., 574
Milligan, B., 329, 330
Milligan, D. E., 159, 645
Mills, J. A., 84
Mills, J. S., 405
Mills, R. H., 323
Milowiz, L., 424
Minasyan, R. V., 760
Minasz, R. J., 644
Minato, H., 451
Minisci, F., 400, 614, 623
Minkin, V. I., 418, 463
Minkoff, G. J., 620
Minton, R. G., 58
Miocque, M., 582
Mirviss, S. B., 890
Misiti, D., 820
Mislow, K., 52, 71, 83, 572
Misono, A., 676
Mitchell, D. L., 871, 872
Mitsch, R. A., 159
Miyasaka, T., 53
Miyazaki, S., 899
Mizsak, S. A., 724
Möbius, K., 196
Mochel, W. E., 158
Mock, W. L., 593
Modena, G., 887
Moelwyn-Hughes, E. A., 316
Moerikofer, A. W., 600
Moffat, J. G., 321, 882
Moffatt, M. E., 129
Moffitt, W., 112
Mohacsi, E., 49, 189
Moiseev, I. I., 823
Moldoványi, L., 864
Molinet, C., 404
Molosnova, V. P., 677
Molyneux, R. J., 53
Momany, F. A., 23
Monack, L. C., 497
Monagle, J. J., 718, 882
Moncrief, J. W., 535
Mondelli, G., 650
Montel, G., 69
Montgomery, L. K., 280, 637, 640
Montino, F., 650
Moodie, R. B., 193
Moon, S., 543, 579, 789
Moore, H. W., 820
Moore, M. L., 669
Moore, P. T., 96, 190, 760
Moore, R. E., 908
Moore, W. R., 96, 122, 165, 190, 648, 760
Moores, M. S., 788
Moormeier, L. F., 608
Morawetz, H., 278
Morgan, K. J., 130
Morganstern, J., 665
Morikawa, M., 436, 609, 616
Morikawa, N., 530
Moritani, I., 159, 160, 645, 739, 741
Moritz, K. L., 390
Morizur, J., 556
Morneweck, S. T., 426
Morrell, C. E., 278
Morris, G. F., 731
Morris, J. W., 489
Morrison, G. A., 101, 107, 109
Morrison, J. D., 91
Morrison, R. T., 530, 552
Morrow, D. F., 120
Morse, B. K., 211, 784
Mortimer, C. T., 26, 53
Morton, J. W., Jr., 468
Mosby, W. L., 440
Moscowitz, A., 112
Moser, W. R., 648
Mosettig, E., 351, 684
Mosher, H. S., 149, 686
Mosher, W. A., 605, 787
Moss, G. E., 308
Moss, R. A., 647

Moss, S. J., 621
Motell, E. L., 534, 848
Moulton, W. N., 861
Mouvier, G., 574, 576
Mowry, D. T., 361, 506, 610, 710
Moyer, C. E., Jr., 440
Moyle, M., 483
Mozingo, R., 351
Muenster, L. J., 221
Muenter, J. S., 20
Mühlbauer, E., 676
Mui, J. Y., 644
Mukai, T., 44, 843
Mulcahy, M. F. R., 790
Müller, A., 762
Müller, E., 317, 333, 547, 647, 811
Müller, G., 590
Müller, H. R., 593, 596
Muller, J., 187
Muller, N., 58, 126, 193
Müllhofer, G., 737, 738
Mulliken, R. S., 58, 68, 126
Mullineaux, R. D., 792
Munk, M. E., 269
Murahashi, S., 159, 160, 645
Murata, I., 49
Murawski, D., 849
Murphy, A. M., 374
Murphy, R. B., 58, 435
Murphy, W. S., 591
Murr, B. L., 216
Murray, K., 593
Murray, M. A., 505
Murray, R. W., 158, 159, 162, 334, 873
Murrell, J. N., 67
Murto, J., 499
Musco, A., 80
Musgrave, O. C., 344
Musgrave, W. K. R., 426
Musher, J., 38, 187
Musker, W. K., 759, 861
Musso, H., 365, 843
Mustafa, A., 641
Myers, J. L., 333
Myers, R. J., 23

Nace, H. R., 748, 757, 758, 882
Nachod, F. C., 168
Naegele, W., 578
Naemura, K., 79
Nagai, Y., 191
Nagakura, S., 171
Naghizadeh, J. H., 58
Nagy, P. L. I., 66
Nahabedian, K. V., 435
Nakabayashi, T., 894
Nakagawa, K., 876
Nakagawa, M., 79, 741
Nakajima, K., 405, 436
Nakanishi, K., 175, 180
Namanworth, E., 135, 136
Naqvi, S. M., 619
Naryschkina, T. I., 861
Nash, E. G., 777
Nasielski, J., 451, 452
Nasipuri, D., 597
Nathan, W. S., 57, 286
Natterstad, J. J., 193
Naudet, M., 535
Nauta, W. T., 433
Nayak, B., 257
Nazarova, I. I., 707
Neale, R. S., 614, 850
Neber, P. W., 816
Necşoiu, I., 348, 881
Needleman, S. B., 627
Neeman, M., 317
Nefedov, O. M., 162
Nehring, R., 613
Neiman, L. A., 44
Neiman, M. B., 154, 342
Nekapetyan, L. A., 645
Nelson, J. A., 658
Nelson, K. L., 388, 401
Nenitzescu, C. D., 67, 348, 412, 463, 616, 881
Nesmeyanov, A. N., 43, 147, 426, 575, 792
Neuman, P. N., 838
Neunhoeffer, O., 502
Neureiter, N. P., 571, 769, 770
Nevitt, T. D., 566
Newall, C. E., 222
Newham, J., 682
Newkome, G. R., 675
Newman, M. S., 68, 80, 129, 207, 278, 363, 567, 632, 677, 701, 819, 895
Newman, P., 83
Nicholas, R. D., 258
Nicholls, B., 67
Nickell, E. C., 873
Nickon, A., 146, 192, 351
Nicolaides, N., 864
Nieboer, H., 93
Nield, E., 611, 765
Nielsen, J., 843
Nielsen, S. D., 545
Nielsen, W. D., 148, 447
Nienhouse, E. J., 600
Niethammer, K., 628
Nieuwenhuis, H. J. W., 545
Nifant'ev, E. Ye., 616
Nightingale, D. V., 434
Nikolenko, L. N., 403, 677
Nikoletić, M., 140, 267
Nilsson, M., 508
Nishimura, J., 648

Nishino, M., 159, 160
Nist, B. J., 187
Nitta, I., 260
Nitzschke, M., 665, 894
Niu, H. Y., 55
Nobis, J. F., 468
Noble, P., Jr., 622
Noël, Y., 55
Noland, W. E., 659
Noll, K., 591, 838
Noller, H., 765
Nomura, Y., 441
Nordlander, J. E., 191
Norin, T., 113
Norman, R. O. C., 376, 387, 388, 395, 396, 403, 404, 406, 413, 426, 498, 539
Norton, H. M., 310
Nosek, J., 354
Noszkó, L., 371, 379
Novikov, S. S., 158, 535, 626, 683, 897
Noyce, D. S., 105, 192, 265, 584
Noyes, R. M., 155, 342
Noyori, R., 509
Nozaki, H., 509
Nozoe, T., 43, 44
Nudenberg, W., 825
Nukada, K., 614
Nukina, S., 373
Nurok, D., 93
Nussim, M., 216
Nyce, J. L., 732
Nye, M. J., 806
Nyholm, R. S., 100
Nystrom, R. F., 593, 812, 893

Oae, S., 372, 373, 403, 500, 501, 901, 907
O'Brien, C., 815
O'Brien, D. F., 142
Occolowitz, J. L., 146
O'Connor, C., 137
O'Connor, D. S., 119
O'Connor, G. L., 748
Oda, R., 726
Odioso, R. C., 830
Oediger, H., 705
Oesterling, R. E., 458
Offermann, K., 778
Ogata, Y., 405, 432, 436, 618, 619, 667, 886, 907
Ogg, R. A., Jr., 117
Ogliaruso, M. A., 42
Ogston, A. G., 289
Ohara, M., 93
O'Hara, R. K., 46
Óhegyi, G., 235
Ohloff, G., 113
Ohno, K., 560
Ohno, M., 614
Ohta, K., 93
Ohta, M., 529, 774, 794
Okada, T., 899
Okamoto, K., 260, 261
Okamoto, M., 614
Okamoto, T., 520
Okamoto, Y., 125, 236, 240, 741
Okano, M., 726
Okazaki, N., 429
Okhlobystin, O. Yu., 476, 768
Ōki, M., 120
O'Konski, C. T., 195, 196
Okumura, A., 429
Okumura, N., 667
Ōkuni, M., 530
Okuzumi, Y., 222
Olah, G. A., 125–129, 135, 136, 138, 193, 258, 379, 381–383, 390, 394, 396–398, 406–409, 411, 413, 415, 416, 418, 420, 424, 425, 433, 434, 439, 463, 513, 608, 908
Olah, J. A., 390, 420, 608
O'Leary, T. P., Jr., 300
Olivares, E., 405
Oliver, J. E., 146
Oliveto, E. P., 611
Ollis, W. D., 55, 481
Olsen, A. R., 252
Olsen, C. J., 791
Ong, J., 832
Onoue, H., 876
Ookuni, I., 802
Openshaw, H. T., 167
Opitz, G., 637
Orchin, M., 168, 173, 645, 861
Ordronneau, C., 135
Orloff, H. D., 104
Orman, S., 530
Orr, B. J., 104
Orttmann, H., 364
Orville-Thomas, W. J., 195
Orzech, C. E., Jr., 193, 786, 789
Osa, T., 676
Osaka, K., 44
Osborn, J. A., 610
Osborne, D. W., 611
Osterholtz, F. D., 561
Ostermayer, F., 773
O'Sullivan, W. I., 299, 685
Oswald, A. A., 578, 588, 886
Oth, J. F. M., 53, 119, 123, 642, 842, 843
Ott, K. H., 835
Ottenheym, J. H., 221
Otvos, J. W., 594
Ötvos, L., 371
Oulevy, G., 415
Ourisson, G., 793
Overberger, C. G., 649, 837

Overchuk, N. A., 382, 383, 390, 411, 434
Overend, W. G., 865
Ovist, E. B. W., 814
Owens, P. J., 557

Packer, J., 222
Padwa, A., 533
Pagano, A. H., 623
Pagano, A. S., 486
Paiaro, G., 80
Pal'm, V. A., 238
Palmer, H. B., 24, 25
Palmer, M. H., 586
Palumbo, R., 80
Pande, K. C., 393
Pandit, U. K., 278
Paneth, F. A., 153
Panunzi, A., 80
Pappalardo, J. A., 331, 670
Pappas, J. J., 871
Pappo, R., 604
Parameswaran, K. N., 676
Parcell, R. F., 816
Parello, J., 188
Parham, W. E., 161, 466, 643, 644, 648
Parini, V. P., 67
Parish, R. C., 322
Park, C. H., 543, 878
Parker, A. C., 110
Parker, A. J., 224, 288, 295, 497
Parker, R. E., 302, 494, 498
Parker, V. D., 425
Parks, C. R., 873
Parmerter, S. M., 460
Parnes, Z. N., 855
Parr, R. G., 103
Pars, H. G., 486
Partch, R. E., 862
Partos, R. D., 42
Pascaru, I., 881
Pascual, O. S., 577
Pasto, D. J., 593, 600
Patai, S., 278, 331, 361, 567, 620, 698, 737
Patel, H. P., 400
Patinkin, S. H., 406
Patrick, J. B., 895
Patterson, A. M., 924, 932, 953
Patterson, W. I., 78
Pattison, F. L. M., 611
Pattison, V. A., 827
Paukstelis, J. V., 668, 723
Paul, D., 405
Paul, M. A., 224, 662
Paul, R., 307, 338
Paulik, F., 442
Pauling, L., 14, 17, 18
Paulsen, H., 862
Pauson, P. L., 43, 44
Pavlath, A. E., 379, 504
Pavlis, R. R., 571, 611
Pawson, B. A., 80
Payne, G. B., 620
Payo-Subiza, E., 187
Pearson, D. E., 240, 346, 411, 475, 675
Pearson, R. E., 536
Pearson, R. G., 202, 208, 212, 222, 230, 287, 293, 326
Pechet, M. M., 850
Peeling, E. R. A., 398
Peer, H. G., 578
Peerdeman, A. F., 83
Pegolotti, J. A., 272
Pegues, E. E., 261
Peiffer, G., 536
Pelah, Z., 894
Pelletier, S. W., 505
Pelter, A., 882
Perelman, M., 724
Perevalova, E. G., 426
Perkampus, H., 380
Perkins, M. J., 551, 552, 570, 643
Perkins, N. A., 411
Perrin, C. L., 138
Perrin, D. D., 221, 228
Peška, J., 361
Peters, D., 47, 59, 117
Peters, D. A. V., 611
Peters, G. A., 664
Peters, J. A., 708
Peters, L. M., 866
Petersen, J. M., 815, 816
Peterson, H. J., 225, 567, 855
Peterson, J. G., 814
Peterson, J. O., 679
Peterson, M., 363
Peterson, M. L., 558
Peterson, P. E., 21, 565, 584, 586
Peterson, R. A., 49
Peto, A. G., 413, 414
Petrarca, A. E., 899
Petree, H. E., 789
Petrov, A. A., 573, 575, 583, 584, 615
Petrov, A. D., 363
Petrovich, J. P., 135
Petterson, R. C., 793, 850
Pettit, G. R., 439, 556, 895, 896
Pettit, R., 40, 50, 51, 66, 119, 837
Pettitt, D. J., 770
Petukhov, G. G., 157
Pews, R. G., 770
Pfeiffer, P., 729
Pfeil, E., 319, 876
Pfitzner, K. E., 882
Pfordte, K., 549
Phadke, R., 423

Philip, H., 790
Philipsborn, W. von, 832
Phillips, B., 619, 865
Phillips, H., 253, 254
Phillips, J. B., 53
Phillips, L., 285
Phillips, R. R., 461
Phillips, W. D., 168, 182, 194
Philpot, J. St. L., 289
Piatak, D. M., 439, 896
Pickard, P. L., 691
Pickering, T. L., 523
Pictet, A., 422
Piercey, M. R., 484
Pierson, W. G., 638
Pietra, F., 491
Piette, L. H., 571
Pilcher, G., 27
Pillai, C. N., 790
Pimentel, G. C., 63, 596
Pinder, A. R., 847
Pines, H., 602, 751, 755, 790, 862
Pink, P., 301
Pinnell, R. P., 534
Pirkle, W. H., 505, 596
Pirogowa, G. N., 753
Pittman, C. U., Jr., 125–129, 135, 136
Pitzer, K. S., 101, 109
Plato, M., 196
Platonov, V. E., 504
Plattner, P. A., 860
Plesske, K., 43
Plieninger, H., 627
Ploss, G., 41
Plotnikova, G. I., 585
Pobiner, H., 870
Pocker, Y., 261, 273, 482, 656, 794, 798, 799
Podstata, J., 501
Pohlke, R., 525
Pohmer, L., 627
Pokrovskii, E. I., 531
Polanyi, M., 310, 595
Pollart, D. F., 755
Pollart, K. A., 872
Pollitt, A. A., 397
Polster, R., 761
Pomerantz, M., 119
Pomeroy, J. H., 675
Pommer, H., 708
Pomponi, A. M., 334
Ponder, B. W., 657
Poole, H. G., 398
Pople, J. A., 182, 193
Popov, E. I., 755
Popov, E. M., 33
Popov, S. I., 677
Popp, F. D., 857
Porfir'eva, Yu. I., 575
Portoghese, P. S., 712
Poshkus, A. C., 374, 825
Posner, J., 49, 806
Poutsma, M. L., 611, 894
Powell, D. L., 55, 65
Powell, J. W., 763
Poynter, W. G., 595
Poziomek, E. J., 154
Praisnar, B., 451
Prater, A. N., 477
Pratt, B. C., 610
Pratt, E. F., 318
Pratt, R. J., 449
Prelog, V., 75, 84, 109, 121, 122, 651, 789
Pressman, D., 729
Pretzer, W., 54
Preuss, H., 569
Price, C. C., 406, 512
Price, E., 244
Priest, W. J., 117
Prikazchikova, L. P., 569
Prilezhaeva, E. N., 587
Prinzbach, H., 119, 467
Pritchard, D. E., 155, 193
Pritchard, H. O., 17
Pritchard, J. G., 812
Privett, O. S., 873
Proskow, S., 74
Prosser, J. H., 498
Pruitt, K. M., 489, 498
Pryor, W. A., 153, 521, 523, 570
Psarras, T., 143, 222
Puckett, J. C., 193
Puerta, J. E., 300
Pullman, A., 28, 55, 391
Pullman, B., 28, 55, 391
Purchase, M., 312
Purlee, E. L., 216, 566
Puterbaugh, W. H., 518, 567, 697
Putnam, W. E., 163
Puttnam, N. A., 429
Pyryalova, P. S., 684

Quadbeck, G., 585
Quan, P. M., 626
Quang, N. M., 389
Quayle, O. R., 310
Queen, A., 261
Quinkert, G., 870
Quinn, R. A., 538
Quiram, E. R., 578
Qureshi, A. A., 666

Raab, G., 475
Rabinovich, E. A., 454
Rabinovitch, B. S., 161

Rabinovitz, M., 603
Rabjohn, N., 880
Radcliffe, L. G., 397
Radda, G. K., 388, 395
Radell, J., 70
Rademacher, L. E., 772
Raecke, B., 436
Rainsford, A. E., 776
Rajan, J. B., 492
Raksha, M. A., 344
Raley, J. H., 792, 793
Ralls, J. W., 568
Ramirez, F., 703
Ramp, F. L., 842
Ramsay, D. A., 168
Ramsay, O. B., 736
Rand, M. H., 656
Randall, E. W., 188
Randall, H. M., 180
Randall, J. J., 494
Rank, B., 868
Rao, C. N. R., 58
Rao, D. V., 637
Raper, W. G. C., 423
Raphael, R. A., 119, 807
Rapoport, H., 37, 896
Rappe, C., 459, 807
Rappoport, Z., 278, 567, 620, 698, 737
Rasmussen, S. E., 413
Rasmusson, G. H., 707
Rathjen, H., 466
Rathore, B. S., 363
Ratuský, J., 436
Rauch, I. E., 876
Raudenbusch, W., 773, 777, 822
Rauhut, M. M., 206, 515
Rausch, D. A., 611
Rausch, M. D., 43, 857
Rawalay, S. S., 866
Ray, K. S., 901
Ray, W. J., 520
Razuvaev, G. A., 549
Read, T. O., 494, 498, 704
Readio, P. D., 525, 536, 579
Rebeller, M., 901
Redlich, O., 70
Redmond, J. W., 817
Redmond, W., 513
Redmore, D., 884
Reed, R., 476
Reed, R. I., 196
Reed, S. F., Jr., 613
Reed, W. L., 622
Rees, C. W., 865
Reese, C. B., 429, 466
Reeves, R. L., 657
Regan, C. M., 41
Rei, M., 137
Reichardt, C., 296
Reid, D. H., 39, 45, 865
Reid, S. T., 187, 790
Reiding, D. J., 433
Reif, L., 434, 470
Reiff, H. E., 648
Reikhsfel'd, V. O., 642
Reilly, E. L., 194
Reimlinger, H., 291
Rein, B. M., 344
Reinheimer, J. D., 498
Reinmuth, O., 149, 353, 471, 555, 684
Reinstein, J. A., 278
Reisch, J., 588, 590
Reitz, O., 215
Rekasheva, A. F., 682
Remanick, A., 137
Rembaum, A., 3, 30
Remizova, T. B., 802
Renk, E., 529, 776
Rerick, M. N., 350, 899
Resnick, P., 461
Reusch, W., 894
Reutov, O. A., 75, 442, 451, 473, 788, 789
Reuwer, J. F., Jr., 215, 237
Reynhart, A. F. A., 426
Reynolds, D. D., 334
Reynolds, G. F., 451
Rhoads, S. J., 830, 834, 836
Rhom, D., 278
Ricca, A., 419
Richards, R. E., 182
Richardson, D. B., 163, 164
Richardson, W. H., 540
Richey, H. G., Jr., 127, 128, 584
Richter, W. J., 458
Rickards, R. W., 820
Rickborn, B., 148, 448, 778
Ridd, J. H., 376, 381, 386, 390, 396, 399, 403, 431, 440, 484–486
Rider, H. D., 342
Riebel, H. J., 843
Rieche, A., 419, 503
Ried, W., 625
Riedel, O., 436
Rieger, A. L., 536
Riemann, J., 437
Riemer, J., 364
Riemschneider, R., 613
Riera, J., 58
Riezebos, G., 873
Rifi, M. R., 43
Rigamonti, J., 513
Riley, T., 457
Rinaldi, C., 833
Rinderknecht, H., 325
Rinehart, K. L., Jr., 80, 688
Riniker, B., 113

Riniker, R., 113
Rinzema, L. C., 665
Riordan, J. C., 225
Ritchie, C. D., 238, 240, 242, 382
Ro, R. S., 771
Roberts, A., 679
Roberts, B. P., 890
Roberts, C. W., 712
Roberts, F. E., 665
Roberts, J. D., 41, 108, 139, 151, 182, 187, 191, 235, 254, 280, 317, 324, 492–494, 497, 529, 636, 639
Roberts, R. M., 406, 410, 433, 434, 832
Roberts, R. M. G., 451
Roberts, W. J., 607
Robertson, J. H., 167
Robertson, J. M., 37, 198
Robertson, P. W., 611
Robertson, R. E., 140, 215, 216, 305
Robertson, W. G. P., 663
Robins, J., 58
Robinson, A. E., Jr., 170
Robinson, B., 844
Robinson, C. H., 611
Robinson, E. A., 420
Robinson, F. P., 845
Robinson, G. C., 259
Robinson, G. M., 844
Robinson, R., 167, 630, 671, 696, 844
Robinson, R. E., 598
Robison, M. M., 638
Roček, J., 541, 864, 870
Rochow, E. G., 148, 442, 470, 476, 583
Rodin, J. O., 631
Roe, A., 513
Rogers, H., 68
Rogers, M. T., 120, 149, 192
Rogić, M. M., 679
Rogowski, F., 21
Rohr, W., 326
Rohrbaugh, P. E., 498
Rokach, J., 606
Romanelli, M. G., 42
Romanet, R., 455
Rømming, C., 69, 484
Ron, A., 486
Ron, M., 216
Rondesvedt, C. S., 552
Roothan, C. C. J., 7
Ropp, G. A., 316
Rose, J. B., 731
Rose, P. I., 193
Rosen, P., 360
Rosenberg, A. M., 312
Rosenberg, R. M., 17
Rosenberger, M., 46
Rosenblum, M., 515, 550
Rosencrantz, D. R., 712
Rosengren, K., 596
Ross, C. B., 712
Ross, R. A., 455
Ross, S. D., 488, 489, 498
Roth, E. A., 23
Roth, H. D., 54
Roth, W. R., 834, 836, 842
Rothman, L. A., 440
Rothrock, H. S., 591
Rothrock, T. S., 801
Rottendorf, H., 505
Roussi, G., 650
Roux, M., 14
Rowe, C. A., Jr., 454
Rozantsev, E. G., 154
Rozantsev, G. G., 158
Rozhkov, I. N., 605, 614
Rubin, R. M., 843
Ruch, R. R., 681
Rüchardt, C., 551, 792
Rudd, E., 616
Rudloff, E. von, 875
Rudolph, J., 310
Rudy, T. P., 531
Ruff, J. K., 612, 884
Rule, H. G., 507
Rummens, F. H. A., 751
Rundel, W., 333
Rundle, R. E., 150
Runge, J., 486
Rusch, R. E., 585
Ruske, W., 424
Russell, G. A., 144, 369, 407, 509, 527, 528, 531, 532, 536, 698, 791, 907
Russell, J. R., 885
Russell, R. L., 400
Russell-Hill, D. Q., 494
Rutherford, K. G., 513, 752, 819
Rutkin, P., 83
Ruzicka, L., 122, 797
Ryan, G., 49
Ryan, J. J., 240
Ryan, P. W., 598
Ryang, M., 689
Rybakova, N. A., 425
Rybin, L. V., 575
Rybinskaya, M. Y., 575
Rylander, P. N., 43
Rytina, A. W., 626

Sabel, A., 884
Sachar, E., 773
Saeed, M. A., 749
Saettone, M. F., 278
Safir, S. R., 363
Safonova, I. L., 645
Sager, W. F., 238, 240, 242, 538

Saha, J. G., 492, 510, 551
Sahyun, M. R. V., 292, 739, 762, 893
Saier, E. L., 65
Saines, G., 225, 855
Saitô, S., 261
Sakla, A. B., 812
Salaman, A. M., 673
Salaün, J., 808
Salem, L., 48
Salinger, R., 143, 222
Salinger, R. M., 149, 151, 475
Salzwedel, M., 482
Samkoff, N., 530, 552
Sammes, P. G., 851
Samuel, D., 516
Samuel, E. L., 423
San, T., 605
Sandberg, R., 312
Sandler, S. R., 800
Sandorfy, C., 175, 181
Sandri, J. M., 722
Saporovskaya, M. B., 93
Sarel, S., 579
Sargent, G. D., 129, 267
Sarkanen, K. V., 438
Sasse, W. H. F., 438, 557
Satchell, D. P. N., 207, 274, 309, 323, 327, 382, 402, 415, 425, 469
Satchell, R. S., 453
Sattler-Dornbacher, S., 689
Sauer, J., 488, 492, 499, 504, 624, 626, 630, 633, 636, 643
Sauer, J. C., 636, 766
Sauermann, D., 612
Sauers, R. R., 861
Saunders, F. C., 530
Saunders, M., 135, 138, 334, 843
Saunders, W. H., Jr., 206, 214, 728, 731, 737, 738, 742, 746, 788
Saus, A., 910
Sauve, D. M., 468, 592, 598
Savedoff, L. G., 288
Saville, B., 330, 588
Savitz, M. L., 561
Sawa, Y., 689
Sawa, Y. K., 505
Sawinski, J., 438
Sawistowska, M. H., 596
Sayce, I. G., 855
Sayigh, A., 254, 879
Sayigh, A. A. R., 719
Sayles, D. C., 354
Scalzi, F. V., 460
Scardiglia, F., 280, 494
Schaad, L. J., 215, 237
Schaefer, A. D., 339
Schaefer, F. C., 664, 673
Schaefer, J. P., 137, 367, 709, 880
Schaeffer, W. D., 74, 292
Schafer, M. E., 493
Schäfer, W., 910
Schaffer, H., 827
Scheben, J. A., 608
Schechter, H., 548
Scheer, J. C., 750
Scheeren, J. W., 416
Scheiner, P., 878
Schellenberg, K. A., 669
Schellenberger, H., 869
Schenker, E., 678
Schenker, K., 121, 481
Schepers, R. G., 850
Scheppele, S. E., 440
Scheraga, H. A., 103
Schertler, P., 119
Schiavelli, M. D., 584
Schiess, P. W., 772
Schijf, R., 416
Schikora, E., 159
Schildknecht, H., 875
Schill, G., 906
Schissler, D. O., 594
Schlag, E. W., 161
Schlatter, M. J., 121
Schlenk, W., 149
Schlenk, W., Jr., 84, 149
Schleyer, P. von R., 20, 65, 129, 138, 139, 193, 258
Schlitt, R., 832
Schlosser, M., 148, 470, 705, 706
Schlubach, H. H., 614
Schmeising, H. N., 33, 58
Schmerling, L., 601, 602, 615
Schmid, G. H., 267
Schmid, H., 830, 832
Schmidlin, J., 605
Schmidt, E. W., 547
Schmidt, G. M. J., 641
Schmidt, K., 654
Schmidt, U., 351
Schmitz, E., 164, 765, 849
Schmitz, R., 505, 606, 897
Schnack, L. G., 286
Schneider, A., 348
Schneider, F., 196
Schneider, W. G., 182, 192
Schnell, H., 422
Schnell, H. W., 128
Schnettler, R. A., 712
Schoeneck, W., 510
Schofield, K., 396
Schöllkopf, U., 163, 444, 529, 644, 702, 704, 827
Schomaker, V., 51
Schönberg, A., 722
Schoone, J. C., 167
Schotte, L., 459

Schowen, R. L., 237, 276
Schrage, K., 595
Schrauzer, G. N., 642
Schreck, J. O., 158
Schreiber, J., 324, 864
Schreiber, M. R., 742, 746
Schriesheim, A., 225, 406, 421, 454, 509, 764, 870, 885, 889
Schröder, G., 53, 842, 843, 873, 874
Schroeder, G., 617
Schroll, G., 592
Schröter, R., 592
Schubert, C., 565
Schubert, W. M., 58, 414, 435
Schueller, K., 640
Schugar, H. J., 631
Schulenberg, J. W., 848
Schulte, K. E., 588, 590
Schultz, F., 435
Schultz, H. P., 370, 371, 857
Schultz, J., 876
Schulz, G., 41
Schumacher, E., 43
Schupp, O. E., III, 707
Schüssler, H., 337
Schwab, P. A., 621
Schwager, I., 529
Schwartz, J. C. P., 168
Schwartz, V., 21
Schwartzman, L. H., 684
Schwarz, M. J., 712
Schwarz, W., 774
Schweizer, E. E., 161, 643, 644, 708, 762
Schwendeman, R. H., 24
Schwetlick, K., 549
Scott, A. D., 252, 312
Scott, A. I., 168
Scott, C. B., 289, 769
Scott, D. A., 148
Scott, M. D., 776, 893
Scott, M. J., 323
Scott, R. A., 103
Scott, W. T., 807
Searle, R., 37
Searles, S., 373
Sears, P. G., 224
Secor, R. M., 94
Sederholm, C. H., 105, 192
Sedlmeier, J., 884
Seebach, D., 119
Seeboth, H., 500, 503
Seide, S., 720
Seidel, B., 637
Seidig, K., 867
Seifried, W., 689
Seijo, E., 696
Selman, S., 803
Seltzer, R., 300, 301
Seltzer, S., 631
Selwitz, C. M., 884
Semenow, D. A., 139, 492, 493, 497
Senders, J. R., 119, 642
Seng, F., 708
Senn, M., 458
Serebryakov, E. P., 559
Sérée de Roch, I., 621
Servis, K. L., 139, 489
Sethna, S., 413, 414, 423, 539
Seubold, F. H., Jr., 790, 791
Seus, E. J., 707
Severin, T., 505, 606, 897
Sevost'yanova, V. V., 535
Seydel, R., 408
Seyferth, D., 348, 466, 475, 644, 648, 703, 704
Shaeffer, W. D., 408
Shah, A. C., 338
Shani, A., 54
Shank, R. S., 648
Shannon, J. S., 861
Shapiro, P., 440
Sharp, D. W. A., 129
Sharts, C. M., 636
Shatavsky, M., 267
Shatenshtein, A. I., 143, 396, 454
Shatkina, T. N., 789
Shaw, R. A., 38, 531, 901
Shchukina, L. A., 477, 852
Shechter, H., 165, 341, 466, 614, 622, 623, 648, 659, 866, 876
Sheehan, J. C., 337, 480, 724
Sheinker, Yu. N., 55, 845
Shelton, J. R., 573, 577, 672
Shemyakin, M. M., 44, 477, 707, 851, 852, 907
Sheppard, N., 32, 67, 129, 175, 192
Sherman, W. V., 560
Sherrill, M. L., 454
Shida, S., 466
Shieh, T., 611
Shillaker, B., 259, 261
Shilov, A. E., 355
Shim, K. S., 119
Shimada, K., 539
Shimagawa, Y., 125
Shimo, K., 340
Shine, H. J., 829, 830, 907
Shiner, V. J., Jr., 215, 216, 268, 478, 682, 731, 773
Shingu, H., 260, 261
Shingū, K., 79
Shiomi, K., 441
Shirley, D. A., 362, 469
Shishido, N., 44
Shnol, S. E., 439
Shoaf, C. J., 684
Shone, R. L., 440
Shono, T., 726

Shoosmith, J., 155, 161
Shoppee, C. W., 267, 579
Shortridge, R. W., 117
Shostakovskii, M. F., 569, 585, 587
Shoulders, B. A., 874
Showell, J. S., 885
Shriner, R. L., 71, 73, 76, 592, 687
Shuekhgeimer, G. A., 626
Shuikin, N. I., 505, 861
Shulgin, A. T., 511
Shull, E. R., 191
Shulman, G. P., 752
Shulman, N., 498
Shumaker, S. H., 821
Shumate, K. M., 838
Shutt, G. R., 254
Sibelle, E. C., 414
Sichels, J. P., 370
Sicher, J., 109, 119, 121, 291, 612, 760, 800
Sidler, J. D., 827
Sieber, R., 884
Sieck, R., 342
Siegmann, R. H., 533
Siew, L. C., 54
Silver, M. S., 139, 141, 268, 278, 739, 785
Silversmith, E. F., 639
Silverstein, R. M., 167
Silverwood, H. A., 861
Sim, G. A., 65
Simamura, O., 191, 530
Sime, J. M., 222
Simmons, H. D., Jr., 644
Simmons, H. E., 54, 637, 648
Simmons, H. E., Jr., 492
Simmons, M. C., 164
Simmons, T. C., 557
Simms, J. A., 569
Simon, H., 737, 738, 761
Simon, W., 382
Simonoff, R., 349
Simons, J. H., 677
Simpson, D. M., 175
Simpson, W. T., 58
Sims, L. L., 579
Singh, G., 644, 704
Singh, H., 529
Singhal, G. H., 754
Sinn, H., 612
Šipoš, F., 291, 800
Sisti, A. J., 438
Sivasankaran, K., 592
Sixma, F. L. J., 402, 412, 750
Skancke, P. N., 108
Skattebøl, L., 645
Skell, P. S., 141, 155, 160–162, 243, 268, 467, 525, 536, 570, 571, 579, 611, 644–646, 736, 746, 748, 755, 785, 788, 800, 888
Skinner, H. A., 17, 27, 945
Skorcz, J. A., 507
Skvarchenko, V. R., 861
Slade, P., 866
Sladkov, A. M., 52
Sladkova, T. A., 683
Slater, C. D., 832
Slates, H. L., 429
Slaugh, L. H., 560, 791–793
Slaymaker, S. C., 163
Sleezer, P. D., 450
Sliam, E., 881
Sloan, M. F., 595
Small, P. A., 396
Smalley, R. K., 324
Smat, R. J., 731
Smentowski, F. J., 798
Smid, J., 147
Smidt, J., 221, 884
Smiles, S., 520
Smiley, R. A., 300
Smissman, E. E., 712, 807, 808
Smit, P., 527
Smit, P. J., 866
Smith, A. J., 759
Smith, A. S., 363
Smith, B., 866
Smith, B. C., 38, 901
Smith, B. H., 80
Smith, B. R., 267
Smith, D. F., 480, 686
Smith, D. M., 552
Smith, F. R., 507
Smith, G. G., 480, 750, 779
Smith, G. V., 595
Smith, H., 597
Smith, J. S., 731
Smith, L. I., 437
Smith, L. R., 341
Smith, M., 321
Smith, M. B., 150, 151, 686
Smith, M. L., 731
Smith, P. A. S., 400, 416, 486, 780, 800, 809, 816, 818–823
Smith, R. D., 648
Smith, R. F., 776, 811
Smith, R. M., 820
Smith, R. P., 611
Smith, R. T., 272
Smith, S., 259, 288
Smith, S. G., 296, 687
Smith, W. B., 559
Smith, W. C., 677
Smith, W. N., 561
Smolinsky, G., 37, 467, 779, 842
Smoot, C. R., 411
Smyth, C. P., 198
Smyth, D. G., 91
Sneen, R. A., 260, 262, 267, 312

Snyder, C. H., 474, 556
Snyder, H. R., 414, 821
Snyder, L. C., 135
Sokolov, V. I., 75, 451
Solenova, S. L., 123
Sollich, W. A., 187
Solovnikov, S. P., 342
Somayajulu, G. R., 23, 33
Sommer, J., 196
Sommer, L. H., 254
Sondheimer, F., 52–55, 194, 549
Sonnenberg, J., 140
Sonntag, N. O. V., 308, 319, 335, 460
Sonoda, N., 538
Sorensen, T. S., 128, 297
Šorm, F., 436
Sorokina, N. P., 845
Sosnovsky, G., 532, 545, 547, 549, 559, 570, 580, 588, 606, 613, 615, 622
Sousa, J. A., 871
Southam, R. M., 292
Southwick, P. L., 814
Spaeth, E. C., 408
Sparapany, J. J., 738
Speakman, J. C., 23
Speiser, S., 486
Spenser, I. D., 777
Speziale, A. J., 341, 344, 701, 705
Spialter, L., 331, 670
Spielman, M. A., 910
Spietschka, E., 810
Spiteller, G., 196
Spiteller-Friedman, M., 196
Spitzer, R., 109
Spitzer, W. C., 490
Spitzin, V. I., 753
Spoerri, P. E., 424
Spokes, G. N., 493
Spotswood, T. M., 423
Sprecher, M., 254, 353
Spring, F. S., 797
Springall, H. D., 53
Sprung, M. M., 429
Spryskov, A. A., 386, 401
Srinivasan, R., 119
Staab, H. A., 314, 326, 353, 416
Stacey, F. W., 570, 580, 588, 611, 613, 622
Stadnichuk, M. D., 615
Stahl, R. E., 80
Stairs, R. A., 881
Staklis, A., 817
Stamhuis, E. J., 583, 658
Standish, N. W., 614
Stanley, J. H., 560
Starcher, P. S., 619, 620
Starer, I., 141, 165, 268, 755, 785, 788
Stark, A., 164
Starnes, W. H., Jr., 878
Starr, L. D., 504
Staskun, B., 684
Staudinger, H., 874
Stefani, A., 575
Stefaniak, L., 193
Stefanovic, D., 737
Steglich, W., 336
Steiner, H., 621
Steinhardt, C. K., 723
Stephens, J. R., 483
Stephens, R., 342, 344, 611, 765
Stephens, R. D., 507, 592
Stern, A., 440
Stern, E. S., 168, 173
Sternberg, H. W., 608
Sternhell, S., 187, 505
Stetter, H., 482
Stevens, C. L., 269, 591, 754, 771
Stevens, I. D. R., 164, 288
Stevens, J. B., 225
Stevens, T. E., 486, 611, 866
Stevens, T. S., 763, 825, 827
Stevens, W., 416
Stevenson, D. P., 408, 594
Stevenson, R., 797
Stewart, E. T., 3
Stewart, F. H. C., 55
Stewart, R., 193, 221, 222, 854, 863, 864, 868
Stewart, R. W., 405
Stewart, W., 196
Stiles, A. W., 353
Stiles, M., 438, 493, 494, 627
Stille, J. K., 621
Stirling, C. J. M., 75, 280
Stivers, E. C., 215, 237
Stock, L. M., 20, 58, 286, 322, 381, 386, 387, 391, 394, 395, 409
Stocken, L. A., 289
Stockmann, H., 630
Stoffelsma, J., 665
Stoicheff, B. P., 21, 32
Stojiljković, A., 866
Stolow, R. D., 106, 108, 759
Stone, E. W., 196
Stone, F. G. A., 44
Stone, R. M., 240
Stork, G., 271, 360, 464, 465, 807
Story, P. R., 65, 135, 546, 873
Stothers, J. B., 182, 188, 215
Stoughton, R. W., 78
Stout, R., 438
Strachan, P., 638
Strachan, W. S., 797
Streitwieser, A., Jr., 3, 21, 28, 30, 41, 74, 142, 216, 218, 222, 251, 254, 259, 263, 281–283, 291, 292, 408, 434, 470
Strickler, P. D., 338
Stroh, R., 408

Struchkov, Yu. T., 123
Strunin, B. N., 768
Struve, W. S., 809
Stucky, G., 150
Stull, D. R., 383
Sturm, E., 41, 53
Sturm, G. P., 323
Stutchbury, J. E., 663
Subba Rao, B. C., 680, 902
Subramanian, P. M., 732
Suchanek, P., 695
Sugamori, S. E., 216
Sugden, S., 286
Suhr, H., 498
Sullivan, J. M., 750
Sullivan, P. J., 153
Sulzbacker, M., 888
Summers, L., 284
Sumrell, G., 611
Sunko, D. E., 140, 267
Suschitzky, H., 324
Sushchinskii, M. M., 181
Susuki, T., 425
Susz, P. B., 415
Suter, C. M., 401
Sutton, L. E., 19, 21, 198
Suvorov, N. N., 845
Suzuki, H., 437, 440
Suzuki, N., 539
Suzuki, S., 216
Svoboda, M., 121, 760
Swain, C. G., 215, 236–238, 261, 289, 317, 888
Swain, P. A., 541
Swamer, F. W., 685
Swan, J. M., 329, 330
Swarmer, F. W., 365
Swart, E. R., 261
Swartzentruber, P., 648
Swartzentruber, P. E., 644
Sweat, F. W., 882
Sweeney, W. A., 414
Swensen, W. E., 704
Swern, D., 618, 885, 886
Swierczewski, G., 650
Swinbourne, E. S., 750
Swindell, R. T., 267
Symons, M. C. R., 58, 196
Synerholm, M. E., 254
Syrkin, Ya. K., 17, 439, 823
Szabo, A. L., 310
Szmant, H. H., 901
Szmuszkovicz, J., 464, 637, 668, 861
Szwarc, M., 24, 523, 575
Szymanski, H. A., 180

Tabuchi, H., 432
Tabushi, I., 619, 886
Tadanier, J., 786
Tadros, W., 812, 908
Taft, R. W., Jr., 35, 238, 243, 244, 314, 492, 566
Taha, I. A. I., 267
Taipale, J., 472
Taits, S. Z., 557
Takahashi, H., 899
Takahashi, J., 268
Takano, Y., 899
Takeshita, T., 20, 732
Takeuchi, K., 261
Talbott, R., 435
Taller, R. A., 187
Tanaka, J., 171, 759
Tanner, D. D., 536, 537
Tanner, H., 336
Tao, E. V. P., 21, 565, 586
Tarao, R., 441
Tarbell, D. S., 385, 830
Tartakovskii, V. A., 683, 897
Tashchuk, K. G., 553
Tatchell, A. R., 91
Tate, D. P., 557
Tatlow, J. C., 342, 344, 495, 611, 765
Tatsumi, S., 91
Taub, B., 535
Taub, D., 405, 429, 619
Taubenest, R., 43
Taurins, A., 673
Tavares, D. F., 299
Taylor, A. F., 230
Taylor, D. R., 573, 578, 765
Taylor, F. M. H., 254
Taylor, H. T., 616
Taylor, J. W., 637
Taylor, L. W., 173
Taylor, R., 376, 386, 387, 396, 403, 406, 413, 426, 750, 779
Taylor, R. C., 498
Taylor, W. C., 622
Tchoubar, B., 807
Tedder, J. M., 399, 400, 436, 527, 529, 537
Telder, A., 402
Temme, H., 505
Terakawa, A., 539
Terao, T., 466
Terent'ev, A. P., 615, 899
ter Maten, G., 453
Terrell, R., 464
Thaler, W., 525, 535
Thaler, W. A., 588
Theaker, G., 400, 436
Thelan, P. J., 849
Theodoropulos, S., 536
Theuer, W., 360
Thiede, R. J., 659
Thier, W., 593, 596
Thomas, B. R., 265
Thomas, C. R., 611

Thomas, H., 598
Thomas, J. A., 430
Thomas, P. J., 750
Thomas, R. J., 276, 277, 315
Thomas, W. A., 194
Thompson, G., 21
Thompson, H. W., 605
Thompson, J. A., 874
Thomson, J. B., 552
Thomson, R. H., 61
Thornton, E. R., 214, 236, 251, 888
Thornton, S. D., 688
Thurmaier, R. J., 565
Thurn, R. D., 731
Thweatt, J. G., 603, 637, 638
Thyagarajan, B. S., 857
Tichý, M., 180, 291, 800
Tieman, C. H., 753
Tien, J. M., 55, 882
Tiers, G. V. D., 187
Till, S. B., 170
Timmons, C. J., 273, 884
Tinsley, S. W., 620
Titov, A. I., 548
Titov, M. I., 701
Titov, Yu. A., 630
Titz, I. N., 862
Tkachuk, R., 41
Tobey, S. W., 277
Tobiason, F. L., 24
Todd, D., 893
Todd, L. J., 648
Todesco, P. E., 887
Toekelt, W. G., 602
Tolbert, T. L., 691
Tolgyesi, W. S., 126, 129, 382, 424, 439, 513
Topley, B., 255
Torigoe, M., 557
Toromanoff, E., 653
Townley, E. R., 851
Towns, D. L., 148
Traetteberg, M., 33
Trager, W. F., 192
Trahanovsky, W. S., 267, 863
Trapnell, B. M. W., 596
Trapp, H., 813
Trautwein, H., 792
Traxler, M. D., 688
Traylor, T. G., 138, 443, 444, 451
Traynelis, V. J., 509, 882
Traynham, J. G., 265, 577, 789
Trecker, D. J., 606, 837
Treffers, H. P., 312
Treiber, A. J. H., 644
Treibs, W., 364, 486
Trepka, R. J., 148
Trevillyan, A. E., 469
Triem, H., 910
Trifan, D., 136
Trippett, S., 356, 370, 702
Trisler, J. C., 830
Tristram, E. W., 675
Trojánek, J., 21
Trost, B. M., 359
Trotman-Dickenson, A. F., 230, 527, 531
Trotter, J., 51
Trottier, C. H., 899
Trozzolo, A. M., 158, 159, 162
Truce, W. E., 279, 280, 374, 417, 520, 557, 569, 649, 665
Trumbull, E. R., 758, 760, 761, 842
Tschuikow-Roux, E., 161
Tsir, Ya., 363
Tsubomura, H., 159, 171
Tsuji, J., 360, 560, 609, 616, 882
Tsuji, N., 505
Tsukamoto, A., 352, 353
Tsunawaki, S., 512
Tsuno, Y., 395
Tsuruta, H., 843
Tsutsui, M., 555
Tsutsumi, S., 425, 538, 689
Tucker, B. G., 790
Tucker, O., 549
Tufariello, J. J., 99, 879
Tuji, T., 645
Tuleen, D. L., 525, 526, 536
Tullock, C. W., 678
Tung, C. C., 701
Turkevich, J., 594
Turley, H. G., 254
Turner, D. W., 168
Turner, J. O., 128, 222
Turney, T. A., 486
Turro, N. J., 119, 806
Tuttle, T. R., 155
Tveten, J. L., 441
Tweedie, V. L., 350, 351
Twigg, G. H., 543
Tyczkowski, E. A., 458

Ucciani, E., 535
Uchida, N., 261
Ugi, I., 725, 778
Uhlig, F., 414, 821
Ulbricht, T. L. V., 92
Ullman, E. F., 516
Ulrich, H., 719
Ulrich, S. E., 354
Ungnade, H. E., 627
Untch, K. G., 54
Urban, R. S., 803
Urbanek, L., 529
Urbánski, T., 193
Urey, H. C., 655
Urry, W. H., 549
Ursprung, J. J., 796

Uthe, J. F., 412
Utley, J. H. P., 386
Uyeda, R. T., 454

Vaichunaite, B. K., 851, 907
Vail, O. R., 681
Valange, P., 119, 123, 642
Valenta, Z., 860
Valicenti, J. A., 771
Valleé, R. E., 65
van Asselt, W. J., 870
Van Atta, R. E., 681
Van Auken, T. V., 80
van Bac, N., 440
van Bekkum, H., 239, 240
van Bommel, A. J., 83
Van Den Berghe, J., 810
Van der Auwera, A., 161
van der Ploeg, H. J., 578
van der Veen, J. M., 420
van der Ven, S., 644
VanderWerf, C. A., 705
van der Zeeuw, A. J., 464
Van Dolah, R. W., 778
van Dorp, D. A., 873
Vane, F. M., 187
Van Eenam, D. N., 518
van Emster, K., 784
van Es, A., 416
van Es, T., 675, 684
Van Hoozer, R., 754
van Krevelen, D. W., 870
van Raayen, W., 221
Van Sickle, D. E., 470, 631
van Tamelen, E. E., 54, 556, 596, 643, 659, 680, 895
van Willigen, J. H. H. G., 93
Vasil'eva, V. F., 55
Vasina, T. V., 653
Vaughan, C. W., 493, 497
Vaughan, J., 222
Vaughan, L. G., 475
Vaughan, W. R., 688
Vaulx, R. L., 517
Veeravagu, P., 713, 746
Veerkamp, T. A., 221
Velluz, L., 114
Venkatasubramanian, N., 863, 864
Venkatesan, K., 120
Venturello, C., 649
Verbang, J. J., 658
Verbeke, G., 534
Verbrugge, C., 556
Verkade, P. E., 239, 240, 349, 354
Vermont, G. B., 530, 552
Verzele, M., 663
Veselovskaia, I. K., 503
Vickery, B., 637
Viehe, H. G., 119, 123, 642, 643, 766
Vieregge, H., 714
Vilkas, M., 366
Vill, J. J., 356
Vincent, B. F., Jr., 683, 898
Vincenzi, F. F., 192
Vinograd, L. Kh., 687
Vinogradov, S. L., 755
Vinogradova, L. P., 871
Viola, A., 835
Vitt, S. V., 93
Vizgert, R. V., 372
Vofsi, D., 613
Vogel, E., 54, 117, 121, 834, 835, 838, 843
Vogel, G., 149
Vogel, W., 221
Vogelfanger, E., 136
Voisey, M. A., 164
Voitsekhovskaya, I. Yu., 338
Volger, H. C., 444, 446
Vollbracht, L., 402
Volod'kin, A. A., 379, 802
Vol'pin, M. E., 37, 44, 49, 646
Volz, H., 50, 128
Vöpel, K. H., 41
Vorbrüggen, H., 324
Vorozhtsov, N. N., Jr., 504
Vossius, D., 818
Vowinkel, E., 318
Vreugdenhil, A. D., 150
Vul'fson, N. S., 687
Vyas, V. A., 737
Vysotskaya, N. A., 539

Waack, R., 469
Wächtershäuser, G., 466
Wadsworth, D. H., 707
Wagner, C. D., 594
Wagner, P., 532
Wagner, R. B., 318
Wagner, R. S., 23
Wagner, W. M., 163, 644
Waight, E. S., 174
Wakabayashi, N., 878
Wakamatsu, S., 340
Wakamatsu, T., 510
Wakefield, B. J., 349, 509
Walborsky, H. M., 445, 476, 483
Waldbillig, J. O., 450
Walden, P., 207, 253
Wale, C. L., 347
Walia, J. S., 791
Walker, D., 385
Walker, D. F., 924
Walker, H., 590
Walker, L. E., 776

Wall, A. A., 737
Wall, M. E., 721
Wallace, T. J., 764, 870, 885, 889
Walling, C., 155, 156, 521, 527, 529, 532–536, 543, 546, 570, 580, 588, 595, 606, 613, 615, 621, 631, 764, 790, 866
Wallis, E. S., 429, 817
Wallis, S. R., 779
Wallwork, S. C., 68
Walsh, A. D., 18, 21, 23, 575
Walsh, E. J., 811
Walsh, E. J., Jr., 351
Walsh, T. D., 259, 263
Walsh, W. L., 814
Walter, D., 827
Walter, W. F., 556
Walters, W. D., 838
Wambsgans, A., 850
Wanders, A. C. M., 439
Wang, C. S., 374
Wang, J. Y. C., 533
Wanzlick, H., 158, 159
Warburton, W. K., 403
Ward, E. R., 484
Ward, H. R., 122, 165
Ward, R. L., 155
Ware, J. C., 405, 451
Waring, C., 878
Warner, C. R., 811
Warner, D. T., 649
Warnhoff, E. W., 795
Warren, J. P., 240
Washburne, S. S., 466
Wasserman, A., 626
Wasserman, E., 50, 81, 158, 159, 162, 905
Wasserman, H. H., 479, 868
Watanabe, H., 44
Watanabe, K., 660
Watanabe, W., 324
Waters, W. A., 541, 543, 550, 854, 857, 863, 865, 868, 870
Watkinson, J. G., 239
Watson, W., 239
Watts, L., 50, 51, 119
Watts, M. L., 344
Watts, W. E., 129, 138, 139, 258
Waugh, J. S., 185
Wawzonek, S., 849
Weaver, W. M., 288
Webb, D., 438
Weber, P., 527
Weber, R., 876
Webster, B., 636, 723
Webster, B. R., 820
Weedon, B. C. L., 558, 590
Weger, E., 595
Wegler, R., 910
Weigmann, H., 706
Weinberg, D. S., 137
Weiner, H., 260, 262
Weiner, M. A., 149
Weiner, S. A., 509
Weingarten, H., 500
Weinheimer, A. J., 593
Weinkauff, O. J., 323
Weinlich, J., 122
Weinstein, S., 737
Weis, C., 156
Weisenborn, F. L., 619
Weiss, A., 529
Weiss, A. W., 7
Weiss, E., 150
Weiss, H. M., 426
Weiss, J., 255
Weiss, K., 554
Weiss, S., 331
Weissberger, A., 168, 205
Weisse, G., 720
Weissenbach, P., 383
Weisser, H. R., 845
Weissermel, K., 613
Weissman, P. M., 352, 893
Weissman, S. I., 155
Weizmann, C., 888
Welch, D. E., 475
Wellman, K. M., 192, 847
Wells, J. N., 672
Wells, P. B., 593
Wells, P. R., 238, 239, 242, 245, 290
Welvart, Z., 215
Wender, I., 608
Wendler, N. L., 429, 795
Wenkert, E., 893
Wentworth, G., 798
Wepster, B. M., 36, 239, 240, 349, 354
Werner, E. A., 331
Werner, H., 66, 466
Werner, N. D., 526
Wescott, L. D., Jr., 161, 646
Wessely, F., 685
West, P., 469
West, R., 55, 65, 149
West W., 168, 175
Westerkamp, J. F., 717
Westhead, E. W., Jr., 278
Westheimer, F. H., 214, 662, 863, 864, 870
Westman, L., 80
Weston, A. W., 401, 483
Weston, R. E., Jr., 216
Wetzel, W. H., 750
Wexler, S., 622
Weyerstahl, P., 327
Weygand, F., 336, 761, 809
Whaley, W. M., 422
Whalley, E., 226, 566
Whang, J. J., 80

Whatley, L. S., 65
Wheeler, D. M. S., 681
Wheeler, O. H., 175, 679, 741, 743, 881
Whelan, W. P., Jr., 254
Wheland, G. W., 21, 28, 39, 41, 59, 65, 71, 86, 91, 153, 490, 781
White, A. M. S., 679
White, E. H., 333
White, E. P., 611
White, H. S., 430
White, J. W., 323
White, R. F. M., 182
White, W. N., 139, 271, 430, 832
Whitehead, M. A., 18
Whitehurst, D. D., 621
Whitesides, G. M., 151
Whitham, G. H., 620
Whiting, M. C., 67, 83, 292, 594, 763
Whitman, G. M., 610
Whitmore, F. C., 292, 686, 782, 784
Whittaker, D., 682, 795
Whittingham, D. J., 255
Wiberg, K. B., 119, 121, 187, 214, 354, 534, 538, 540, 545, 848, 854, 855, 877, 880, 881
Wickliffe, R. A., 642
Wiechell, H., 812
Wiechert, K., 580
Wiedemann, W., 286
Wieland, H., 824
Wieland, P., 75
Wiesboeck, R., 736
Wiest, H., 630, 633
Wightman, R. H., 882
Wijers, H. E., 329
Wilchek, M., 353
Wilde, H., 867
Wilds, A. L., 680, 810
Wiley, D. W., 44, 574, 638
Wiley, G. A., 344
Wiley, R. H., 192
Wilhelm, M., 300
Wilkins, R. G., 76
Wilkinson, G., 43, 610
Wilkison, W. W., 741, 746
Willard, J. E., 533
Willi, A. V., 435
Williams, D. H., 182, 196, 894
Williams, D. J., 790
Williams, D. L. H., 430
Williams, E. D., 681
Williams, F. P., 510
Williams, F. T., Jr., 659
Williams, F. V., 230
Williams, G. H., 523, 530, 538, 549–551
Williams, J., 149
Williams, J. F. A., 59
Williams, J. K., 638
Williams, L. P., Jr., 798
Williams, M. J. G., 76
Williams, N. R., 505
Williams, P. H., 620, 823
Williams, R. J., 748
Williams, R. O., 192, 609
Williamson, K. L., 192, 193
Willis, J. B., 286
Wilmshurst, J. R., 790
Wilshire, J. F. K., 558
Wilson, A., 117, 636
Wilson, C. L., 446
Wilson, C. V., 559, 617
Wilson, E. B., 23, 103, 182
Wilson, E. R., 122
Wilson, G. E., 637
Wilson, G. J., 655
Wilson, J. M., 197
Wilson, J. N., 594
Wilson, M. K., 175
Wilson, R., 492
Wilt, M. H., 435
Wilt, J. W., 790
Wilzbach, K. E., 119
Wims, A. I., 877
Win, H., 382
Wineman, R. J., 334
Winestock, C. H., 810
Wingler, F., 648
Wingrove, A. S., 148, 448
Winikov, E. H., 240
Winkelmann, E. H., 535
Winkler, H., 476
Winkler, H. J. S., 80, 476
Winstein, S., 108, 119, 135–137, 140, 259, 264, 266–268, 270, 288, 296, 297, 302, 345, 443, 444, 450, 545, 618, 729, 735, 738, 784, 786, 790
Winter, R. A. E., 768
Winter, R. E. K., 838
Winterfeldt, E., 569
Wippel, H. G., 440, 705
Wisaksono, W. W., 872
Wiseman, E. H., 611
Wisotsky, M. J., 127–129, 221
Witanowski, M., 151, 193
Witkop, B., 895
Witschard, G., 708
Witt, O. N., 383
Wittig, G., 122, 149, 163, 492, 494, 627, 628, 648, 695, 702, 704, 706, 708, 761, 769, 827
Wittman, J. W., 559
Wohl, J., 605
Wojtkowiak, B., 455
Wolf, D. C., 816
Wolfe, J. R., Jr., 263
Wolfenden, J. H., 396
Wolff, H., 819
Wolff, M. E., 849

Wolford, R. K., 224
Wolinsky, J., 712, 841
Wolovsky, R., 52–54, 194, 549
Wolter, D., 549
Wolthius, E., 894
Wong, E. W. C., 786
Wood, J. L., 175
Wood, L. L., Jr., 677
Wood, N. F., 307
Woodall, N. B., 175
Woodgate, P. D., 893
Woodruff, C., 443
Woods, G. F., 145
Woodward, R. B., 112, 423, 481, 631, 633, 635, 837, 839
Woodworth, R. C., 160, 644, 646
Woolf, L. I., 744, 746
Woolhouse, R. A., 428, 429
Woolsey, N. F., 559, 810
Worden, L. R., 352
Work, S. D., 299
Worosz, J. C., 237, 238
Wotiz, J. H., 151, 455, 498
Wright, G. A., 486
Wright, G. F., 40, 106, 605
Wu, C., 405, 412
Wu, C. Y., 140, 221, 222
Wu, G., 297, 459
Wunderlich, D., 602
Wunderlich, K., 514
Wyatt, R. E., 103
Wyman, B. M., 611
Wyman, D. P., 459, 533
Wyman, G. M., 97
Wynberg, H., 37, 75, 419
Wynne-Jones, K. M. A., 656
Wysocki, D. C., 54

Xuong, N. D., 440

Yager, B. J., 682
Yager, W. A., 50, 158, 162
Yakerson, V. I., 439
Yakobson, G. G., 498, 504, 513
Yakushin, F. S., 215
Yakushina, L. M., 587
Yale, H. L., 819
Yamada, H., 260
Yamagami, M., 907
Yamakawa, M., 44
Yamamoto, Y., 160, 509
Yamase, Y., 413, 415
Yamazaki, H., 348
Yan, T., 408
Yang, D. H., 712
Yang, N. C., 472, 611, 712
Yanovskaya, L. A., 702, 707
Yao, H. C., 461
Yarovenko, O. N. N., 344
Yashunskii, V. G., 55
Yates, B. L., 139, 239, 779
Yates, K., 221, 222, 225, 459
Yates, P., 630
Yats, L. D., 433
Yen, V. Q., 582, 616
Yoon, N. M., 893
Yorka, K. V., 301
Yoshida, K., 432
Yoshida, M., 54
Young, A. E., 49, 445, 476
Young, D. P., 783
Young, J. A., 716
Young, J. E., Jr., 23
Young, J. F., 610
Young, L. B., 863
Young, R. J., 869
Young, W. G., 270–272, 284, 450, 729
Youssefyeh, R. D., 464, 873
Yufit, S. S., 110
Yukawa, Y., 395
Yukhomenko, M. M., 615
Yung, Y. H., 240
Yur'ev, Yu. K., 569
Yur'eva, L. P., 426

Zabicky, J., 411
Zabriskie, J. L., 505
Zahler, R. E., 488, 519
Zahn, H., 337
Zahradnik, R., 47
Zakharkin, L. I., 352, 476, 684, 768
Zalar, F. V., 483
Zalesskaya, T. E., 802
Zalut, C., 403
Zander, M., 40
Zanet, P. M., 561
Zanger, M., 705
Zaugg, H. E., 289, 339, 668, 723
Závada, J., 121, 612, 760
Zaviolov, S. I., 871
Zefirov, N. S., 569, 582
Zelinskii, N. D., 862
Zenner, K., 319, 514
Zergenyi, J., 777, 822
Zhmurova, I. N., 338
Ziegenbein, W., 760
Ziegler, E., 424
Ziegler, K., 767
Zil'berman, E. N., 424, 425, 660, 661, 664, 684, 715
Zimmering, P. E., 278
Zimmerman, H., 310
Zimmerman, H. E., 517, 688, 701, 775, 798, 825

Zimmerman, J. E., 307
Zimmerman, S. E., 737
Zinn, J., 109
Zollinger, H., 317, 377, 378, 382, 399, 431, 484, 491, 552, 553
Zoltewicz, J. A., 498
Zook, H. D., 146, 289, 318, 480, 686
Zucker, L., 225
Zwanenburg, B., 807
Zweifel, G., 593, 599, 600, 814
Zweig, A., 798

Subject Index

$A_{AC}1$ mechanism, 310–313, 315, 321, 322
$A_{AC}2$ mechanism, 310–314, 321
$A_{AL}1$ mechanism, 310–313, 315, 321
$A_{AL}2$ mechanism, 310–313
Abietic acid, 921
Absolute configuration. 82
Abstraction, by free radicals, 157, 523–529
  of hydride ions, 855
  internal, 542, 793, 849, 851
Abstract publications, 939–941
Acenaphthylene, 566
Acenaphthylene deuterium bromide, 566
Acetaldehyde, condensation with formaldehyde, 702
  formation of, 582, 884
  in the haloform reaction, 482
  hydration of, 655
  polymerization of, 717
  reaction with ammonia, 667
Acetals, acylation of, 464
  bromination of, 459
  conversion to enol ethers, 756
  formation of, 316, 318, 350, 355, 585, 661–663, 711, 717 (*see also* 956)
  formylation of, 464
  hydrolysis of, 306
  oxidation of, 865
  reaction, with epoxides, 319
    with organometallic compounds, 355, 363
  reduction of, 350
  transetherification of, 318
Acetamide, 275
1-Acetamido-2-ethoxynaphthalene, 390
Acetic acid, as an acidic solvent, 223
  acidity of, 19
  decarboxylation of, 477
  hydrogen bonding in, 64
  in nitrile formation, 675
  reaction with cyclopropylalkenes, 579
Acetic anhydride, in dehydrations, 325, 587, 757, 776
  formation of, 587
  in formylation of amines, 336
  hydrolysis of, 309
  reaction, with acetals, 464
    with phthalic anhydride, 699
Acetoacetic ester (*see* Ethyl acetoacetate)
Acetoacetic ester synthesis, 358, 359
Acetolysis rates, calculated, 139
Acetone, condensation reactions, 173, 697
  formation of, 680, 681, 864
  hydration of, 655
Acetone, in Mannich reaction, 671
  oxidation of alcohols, 863
  reaction with carbene, 811
Acetone hydrate, formation of, 655
Acetophenone, 685, 911
Acetophenone-N-butylimine, 911
Acetoxime, 586
2-Acetoxy-6-bromocyclohexanone, 847
2-Acetoxy-2-cyclohexanone, 847
1-Acetoxy-1,2-diphenylethane, 748
3β-Acetoxy-5α-methylsulfinylcholestane, 749
N-Acetylaminomalonic ester, 358
Acetylation of alkylbenzenes, 381, 391
Acetylbromofluorobenzenes, 389
Acetyl chloride, 415
1-Acetyl-1-chloro-2-methylcyclohexanes, 807
2-Acetyl-1-chloro-1,1a,2,6b-tetrahydro-6b-methylcycloprop[b]indole, 648
3-Acetyl-9,10-dihydrophenanthrene, 877
Acetylene, acidity of, 145
  acylation of, 369
  addition of RH, 607
  alkylation of, 361
  in alkylation of aromatic rings, 407
  arylation of, 552
  bond angles of, 14
  conversion, to unsaturated esters, 649
    to vinylacetylene, 603
  hydration of, 582
  in nmr, 184
  reaction, with carbenes, 646
    with Grignard reagents, 440
    with hydrogen cyanide, 610
    with nitromethane, 606
  tetramerization, 642
  trimerization, 642
Acetylenes (*see* Alkynes)
Acetylenic acid esters and amides, cleavage of, 483
Acetylenic acids, 477
Acetylenic ethers, formation of, 766
  hydration of, 583
  ozonization of, 872
Acetylenic thioethers, hydration of, 583
3-Acetyl-2-hydroxyindole, 507
Acetyl nitrate, 396, 623
Acid-base theory, 217–230
Acid catalysis, 226
Acids (*see* Carboxylic acids; Sulfonic acids; etc.)
Acid solvents, 222
Acid strengths, 217–222
  of carbon acids, 142

Acid strengths, of carboxylic acids, 19, 20
  determination of, 194, 469, 470
  effects of medium on, 229
  effects of structure on, 228
  of positive ions, 145
  of squaric acid, 55
  tables of, 20, 219–221
Aci form, of nitro compounds, 62, 659
Acridone, 414
Acrolein, 423
Acrylic acid, 629
Acrylonitrile, as a dienophile, 626*n.*
  dimerization of, 636, 638
  formation of, 610
  Michael-type reactions of, 465, 568, 585*n.*, 586, 588*n.*, 590*n.*
Activated complex, definition of, 203
Activating groups, in electrophilic aromatic substitution, 382, 385–387, 389
  in nucleophilic aromatic substitution, 495, 496
Activation free energy, 202
Activation volume, 138
Active hydrogen, definition of, 471
Active hydrogen compounds, acylation of, 364–365
  addition to multiple bonds, 568, 575, 577, 604, 606, 607
  alkylation of, 357–361
  arylation of, 506
  condensation, with aldehydes, 697
    with ketones, 697
    with nitriles, 709
  conversion to enolate ions, 470
  formation of, 364–369
  in Mannich reaction, 670
  nitration of, 547, 548
  nitrosation of, 462
  reaction, with acyl peroxides, 472
    with diazonium ions, 460
    with nitroso compounds, 462
Acylals, formation of, 587, 716, 879, 881 (*see also* 956)
Acylation, of alcohols, 319–323
  of aldehydes, 716
  at aliphatic carbon, 362–372
  of alkenes, 463
  of ammonia and amines, 335–339, 847
  of aromatic rings, 409, 413–415, 424, 433
  of carboxylic acids, 324–325
  of enamines, 465, 482
  of ketones, 716
  of nitriles, 716
  (*See also* Friedel-Crafts acylation)
C-Acylation versus O-Acylation, 298
N-Acylation of amides and imides, 340
Acyl azides, 782
N-Acylaziridines, 353
Acyl bromides, 343, 716
Acylcarbenes, 161, 165, 809
Acyl cations, 129
  cleavage of, 316
  in Friedel-Crafts acylation, 415
Acyl chlorides, reaction with sulfur tetrafluoride, 677
Acyl cleavage, 481–483
Acyl cyanides, formation of, 370
Acyl fluorides, formation of, 343, 678
N-Acylglycines, 699
Acyl halides, in acylation of aromatic rings, 413–415
  addition to multiple bonds, 607, 616
  in Arndt-Eistert synthesis, 809
  conversion, to amides, 335
    to anhydrides, 324
    to azides, 341
    to carboxylic acids, 308
    to carboxylic esters, 319
    to imides, 340
    to ketenes, 638, 766
    to peroxides, 326
    to Reissert compounds, 352
    to thiol acids and esters, 329
  decarbonylation of, 560
  in ether cleavage, 345
  exchange, with acids, 347
    with amides, 335
    with anhydrides, 324
    with esters, 347
  formation of, 343, 346, 347, 538, 581, 616 (*see also* 956)
  halogenation of, 460
  reaction, with active hydrogen compounds, 364
    with alkenes, 463
    with copper cyanide, 370
    with cyanate ions, 342
    with diazomethane, 370
    with enamines, 465, 482
    with free radicals, 528
    with lead thiocyanate, 416
    with mercaptans, 665
    with organometallic compounds, 362, 689
    with phosphoranes, 369
    with sulfur tetrafluoride, 677
    with thiocyanate ions, 342, 416
  reduction of, 351, 897
Acyl hypohalites, 560
Acyl iodides, 343
Acyl isocyanates, 341, 342, 416, 719
Acyloin condensation, 904
Acylonium hexafluoroantimonates, 415
Acyloxy amides, 725
Acyloxylation, 426, 545
Acylphenols, 428
Acyl rearrangements, 845
Acyl sulfonylhydrazides, 353

N-Acylureas (*see* Ureides)
O-Acylureas, 322
1-Adamantyl cation, 129, 258
1-Adamantyl compounds, 258
Addition, to carbon-carbon multiple bonds, 562–650, 711–713, 723–724
    of arenes, 406
    of aryl chlorides, 552
    of carbonium ions, 141
  to carbon-hetero multiple bonds, 651–726
  to carbon-oxygen double bonds, stereochemistry, 90, 651
  to multiple bonds, 200, 202
    of carbenes, 160–164
    of free radicals, 157
Addition compounds, 65–70
Addition-elimination mechanism, in electrophilic substitution, 401, 463
  in free radical arylation, 552
  in nucleophilic substitution, 280, 501, 503, 505, 509
  in oxidations, 856
1,2-Addition reactions, 568, 572, 604
1,4-Addition reactions, 568, 572, 604
Additive dimerization, 558
Additive names, 921
Adipic acid, 870, 871
Air (*see* Autoxidation; Oxygen)
Alane, in reduction of carbonyl bonds, 593
  selectivity, 892
Alane-aluminum chloride, 897
Alanine, 85
Alcohols, acidity of, 219, 228
  addition to multiple bonds, 584, 606, 607, 661
  in alkylation of aromatic rings, 406–409, 411
  in Ardnt-Eistert synthesis, 809
  cleavage of, 480, 824
  conversion, to alkenes, 753
    to alkyl halides, 343
    to amines, 332
    to esters, 319–323, 326
    to ethers, 316–319, 323, 500
    to hydroperoxides, 326
    to nitriles, 866
    to peroxides, 326
    to stable carbonium ions, 126, 128
    to sulfides, 328
    to tetrahydrofurans, 542
  coupling of, 888
  formation of, 303, 305–307, 309–313, 315, 318, 322, 325, 338, 344, 350, 355, 407, 421, 471, 538, 581, 593, 607, 610, 678–682, 684–689, 691, 697, 713, 755, 758, 794, 800, 824, 827, 871, 878, 888, 894–897, 901, 902, 909 (*see also* 956)
  fragmentation of, 772
  in haloform reaction, 482
  in hydrocarboxylation, 609
Alcohols, in Mannich reaction, 670
  mass spectra, 197
  oxidation of, 862–865, 883
  oxidative cleavage of, 870
  pyrolysis of, 757
  reaction, with acetylene, halides and CO, 649
    with aldehydes or ketones and hydrogen halides, 676
    with aryl iodides and nickel carbonyl, 507
    with aziridines, 319
    with carbon disulfide, 664, 757
    with carboxylic esters, 322, 846
    with formic acid, 663
    with hydrazoic acid, 820
    with imino ester salts, 664
    with isocyanates, 663
    with nitriles, 664, 715
    with sulfonamides, 373
    with sulfonyl halides, 373
    with thionyl chloride, 269, 343
  rearrangement of, 794–798
  reduction of, 349
  in reduction of alcohols, 349
  reductive alkylation of, 663
  resolution of, 93
  in transesterification, 322
  in transetherification, 318
Alcoholysis, of acids, 321
  of acyl halides, 319
  of amides, 323, 847
  of anhydrides, 320
  of epoxides, 319
  of esters, 322
  of nitriles, 664
Aldehyde ammonias, 666
Aldehydes, acylation of, 364, 716
  addition, to aldehydes, 717
    to alkenes, 604, 606, 607
  addition reactions, mechanism, 652
  alkylation of, 357
  benzoin condensation of, 714
  Cannizzaro reaction of, 908
  condensations, with active hydrogen compounds, 697
    with N-acylglycine, 699
    with aldehydes, 692–695, 697, 701
    with anhydrides, 698
    with aromatic rings, 421–424
    with esters, 696, 697
    with halo esters, 700
    with ketones, 695, 697
    with phosphoranes, 702–709
  conversion, to acyl halides, 538
    to anhydrides, 545
    to dihalides, 677
    to epoxides, 720
    to α-halo ethers and alcohols, 676
    to nitriles, 675, 867

Aldehydes, conversion, to oximes, 238, 675
    to phenols, 878
  coupling of, 549
  cycloadditions, 723
  decarbonylation of, 435, 560, 790
  enolization of, 457
  formation of, 303, 306, 307, 351–353, 363, 371, 416–420, 438, 458, 478, 561, 582, 600, 609, 656–659, 684, 754, 756, 773–776, 778–779, 798, 801–802, 811, 817, 824, 850, 862–865, 867–868, 871–875, 880–884 (*see also* 957)
  in haloalkylation of aromatic rings, 424
  halogenation of, 458
  in Mannich reaction, 670
  oxidation of, 539–541, 544, 880
  in Passerini reaction, 725
  reaction, with alcohols, 661
    with alkenes, 711
    with alkynyl ethers, 713
    with amides, 668
    with amines, 238, 667
    with ammonia, 666, 710
    with bisulfite ion, 665
    with cyanide ion, 710
    with diazoalkanes, 810
    with hydrazine derivatives, 238, 674, 844
    with hydrogen sulfide, 665
    with ketene, 585
    with mercaptans, 665
    with nitriles, 717
    with organometallic compounds, 92, 684
    with oxazolones, 700
    with peroxy compounds, 823
    with water, 655
  rearrangements of, 801–802
  reduction of, 678, 891–894, 903
  in reductive alkylation, 663, 668
  in Reformatsky reaction, 687
  resolution of, 93
  sulfonation of, 462
  Tishchenko reaction of, 910
  (*See also* Dialdehydes; Unsaturated aldehydes; etc.)
Aldimines (*see* Imines)
Aldohexoses, 88
Aldol, 694
Aldol condensation, 173, 692–695, 701
Aldoses, conversion to furfural, 318
Aldoximes (*see* Oximes)
Aliphatic substitution (*see* Electrophilic substitution; Free radical substitution; Nucleophilic substitution)
Alkali fusion of aryl sulfonates, 500, 502
Alkaloids, rearrangement of, 795*n*.
Alkanes, acylation of, 463
  in alkylation of aromatic rings, 407
  chlorosulfenation of, 547
Alkanes, chlorosulfonation of, 546
  electronic spectra of, 171
  exchange of hydrogen, 594
  formation of, 164, 348–351, 353–355, 438, 466–468, 470, 477, 480, 483, 555–558, 560, 580, 591–599, 601, 607, 686, 867, 876, 891–894, 900 (*see also* 958)
  halogenation of, 532
  nitration of, 547
  oxidation of, 538, 543, 545
  reaction, with alkenes, 601
    with carbenes, 164, 466
    with free radicals, 527
  rearrangement of, 796
  in reduction of alkyl halides, 348
  (*See also* Cycloalkanes)
Alkenes, acylation of, 463
  acyloxylation of, 545
  addition, of aldehydes, 723
    of hydrogen cyanide, 610
    of hydrogen halides, 580
    of hypochlorites, 612
    of hypohalous acids, 612
    of inorganic acids, 584
    of ketones, 723
    of nitrogen compounds, 586, 589, 622–623
    of organometallic compounds, 650
    of RCOOH, 568
    of RH, 601
    of ROH, 584
    of sulfur compounds, 584, 587, 589, 613
    of water, 581
  addition reactions, mechanisms, 562–573
    orientation and reactivity, 573–579
  in alkylation of aromatic rings, 406, 409, 411
  allylic halogenation of, 535
  arylation of, 552
  bond angles in, 14*n*.
  cleavage, with diazonium ions, 876
    with hydrazide ions, 876
  conversion, to acyl halides, 616
    to alkyl halides, 615
    to aryl halides, 615
    to halo nitrogen compounds, 613
    to peroxides, 545
    to sulfonic acids, 885
  Diels-Alder reactions of, 626–636
  dimerization, 556, 633–641
  1,3-dipolar addition to, 623
  electronic spectra of, 173
  epoxidation of, 617, 618
  equilibrium with boranes, 766
  formation of, 307, 345, 453–456, 477, 478, 552, 557, 559, 594, 597–599, 602, 615, 679, 685, 692, 697, 699, 702–709, 727–776, 794–798, 812, 838, 879, 887, 893 (*see also* 959)
  formylation of, 463

- Alkenes, halogenation of, 610
  - hydroboration of, 599
  - hydrocarboxylation of, 608
  - hydroformylation of, 609
  - hydrogenation of, 591–596
  - hydroxylation of, 616
  - Michael addition to, 603
  - nitration of, 547
  - oxidation of, 544, 883–884
  - oxidative cleavage of, 875
  - ozonolysis of, 871–874
  - π-complexes of, 66, 67, 566
  - reaction with aldehydes, 711
    - with carbenes and carbenoids, 643–649
    - with free radicals, 527
    - with hydrazoic acid, 820
    - with ketones, 713
    - with mercuric salts, 583
    - with phosphines, 703
  - rearrangement of, 796–797
  - reduction of, 591–596, 598
  - reductive coupling of, 607
  - in Ritter reaction, 715
  - stability of, 739
  - structure of, 13
  - (*See also* Cycloalkenes; Dienes; etc.)
- Alkoxide ions, in benzil-benzilic ester rearrangement, 803
  - cleavage of, 447, 480
  - in Favorskii rearrangement, 804
  - reaction with chloro alkenes, 762
- α-Alkoxy hydroperoxides, 873
- β-Alkoxy isocyanates, 591
- Alkylarylamines, alkylation of, 358
- Alkylation, of acids, 323, 324
  - of alcohols, 316–318
  - at aliphatic carbon, 353–362
  - of aromatic compounds, 383, 406–412, 509, 553
    - reversal of, 433
  - of ammonia and amines, 331–334
  - of enamines, 464
  - of ketones, 357–360, 464
  - of nitrogen heterocycles, 509, 690
  - of oximes, 327
  - (*See also* Friedel-Crafts alkylation)
- C-Alkylation versus O-alkylation, 298, 300–301
- N-Alkylation of amides and imides, 340
- Alkyl borates, conversion to alcohols, 305
  - formation of, 680, 889
  - pyrolysis of, 758
- Alkyl bromides, bromination of, 525
  - solvolysis rates, 282
- Alkyl chloroformates, 269, 882
- Alkyl chlorosulfites, 269, 324
- Alkyldiphenylphosphine oxides, 705
- Alkyl fluorides, formation of, 342, 344
  - reaction with antimony pentasulfide, 126, 127
- Alkyl groups, as neighboring groups, 267
- Alkyl halides, addition to multiple bonds, 606, 614
  - in alkylation, of aromatic rings, 406, 408–412
    - of enamines, 464
  - in amine rearrangements, 432
  - conversion, to alkenes, 741, 744, 747, 750, 751, 765, 887–888
    - to azides, 341
    - to ethers, 233, 316
    - to Grignard reagents, 149, 475
    - to hydroperoxides, 325
    - to inorganic esters, 327
    - to peroxides, 325
  - coupling of, 353–355, 887
  - exchange with alkyllithium compounds, 142
  - formation of, 269, 342–346, 348, 406, 424, 473, 476, 532–537, 559, 560, 580, 607, 610–616, 777 (*see also* 960)
  - fragmentation of, 772
  - hydrolysis of, 233, 234, 303, 471
  - oxidation to aldehydes, 882
  - oxidative dimerization of, 887–888
  - reaction, with acetylene and carbon monoxide, 650
    - with acetylide ions, 361
    - with acid salts, 323
    - with active hydrogen compounds, 357–361
    - with alkyl phosphites, 705
    - with amide salts, 340
    - with ammonia and amines, 331
    - with cyanate ions, 342
    - with cyanide ions, 361
    - with halide ions, 342
    - with hexamethylenetetramine, 332
    - with metals, 354, 475
    - with nitrite ion, 341
    - with organometallic compounds, 353, 476
    - with oximes, 327
    - with phenols, 301
    - with phosphines, 332, 702
    - with silver nitrate, 327
    - with sodium, 354
    - with sulfur compounds, 328–330
    - with thiocyanate ion, 342
  - reduction of, 348, 471
  - (*See also* Dihalides; Halo ketones; etc.)
- Alkyl hypochlorites, 726
- Alkylmercuric chlorides, 471
- Alkyl nitrates, conversion to alcohols, 305
  - formation of, 326, 327
  - hydrolysis of, 778
- Alkyl nitrites, conversion to alcohols, 305
  - formation of, 300, 326, 327, 341
  - in nitration, 548
  - photolysis of, 850
  - reaction with active hydrogen compounds, 462

2-Alkyloxazol-5-ones, 699
Alkyloxylation, 545
N-Alkyl-N,S-(*o*-phenylene)aminosulfhydrylcarbenes, 159
Alkyl phosphates, formation of, 305, 326
Alkyl phosphites, 305, 705
Alkylpyridines in Mannich reaction, 670
N-Alkylpyridinium salts, 124, 683
Alkylquinolines, formation of, 690
Alkyl sulfates, in alkylation of aromatic rings, 407
  conversion, to alcohols, 305
    to ethers, 317
    to halides, 343
    to peroxy compounds, 326
  formation of, 326, 584
  pyrolysis of, 758
  reaction, with acetylides, 361
    with acid salts, 324
    with active hydrogen compounds, 360
    with amide salts, 340
    with ammonia and amines, 331
    with cyanide ions, 361
    with Grignard reagents, 355
    with oximes, 327
    with sulfur compounds, 328, 330
Alkyl sulfites, conversion to alcohols, 305
  formation of, 326
  pyrolysis of, 758
Alkyl sulfonamates, 333
Alkyl sulfonates (*see* Sulfonic acid esters)
Alkylsulfuric acids, formation of, 581, 584
Alkyltris(dimethylamino)phosphonium salts, 705
Alkynes, acidity of, 221, 229
  addition, of acyl halides, 616
    of alkyl halides, 615
    to alkynes, 603
    to enamines, 603
    of hydrogen cyanide, 610
    of hydrogen halides, 580
    of hypochlorites, 613
    of hypohalous acids, 612
    of nitrogen compounds, 590, 614, 622
    of RCOOH, 587
    of ROH, 585
    of sulfur compounds, 588
    of water, 582
  addition reactions, mechanisms, 563–573
    reactivity, 575
    orientation, 576
  alkylation of, 361
  in alkylation of aromatic rings, 407
  allylic bromination of, 535
  arylation of, 552
  bromination of, 612
  condensation with aldehydes or ketones, 697
  coupling of, 549
Alkynes, 2 + 2 cycloadditions of, 637, 638, 640
  Diels-Alder reactions of, 626
  1,3-dipolar addition to, 625
  formation of, 361, 455, 483, 507, 549, 727, 728, 731, 736, 753, 760, 764, 765, 771, 774, 811 (*see also* 960)
  haloformylation of, 616
  hydroboration of, 600
  hydrocarboxylation of, 608
  hydrogenation of, 593, 594
  hydrogen bonding of, 65
  in Mannich reaction, 670
  Michael addition of, 606
  in nmr, 184
  oxidative cleavage of, 875
  ozonolysis of, 872, 874
  reaction, with boranes, 767
    with carbenes and carbenoids, 646, 648
    with halides and CO, 649
    with Grignard reagents, 440, 469
    with peroxides, 621
  structure of, 14
  tetramerization of, 642
  trimerization of, 642
Alkynyl ethers, 713, 766
Alkynyl halides, 550
Alkynyl Grignard reagents, formation of, 469
Allenes, addition reactions of, 578, 614
  conversion to cyclobutanes, 636, 637
  cyclic, 122
  Diels-Alder reactions of, 627
  formation of, 165, 644, 646, 709, 765, 771
  halogenation of, 612
  hydration of, 584
  hydrogenation of, 594
  isomerism of, 79, 96
  optical activity of, 78, 83
  reaction with carbenes, 645
Allenic aldehydes, formation of, 833
Allyl alcohol, 833
Allylarylamines, 833
Allyl aryl ethers, rearrangement of, 830–834
Allyl aryl thioethers, 833
Allylbenzene, 454
Allylbenzyldimethylammonium ions, 826
Allylbenzylmethylphenylammonium iodide, 826
Allylcarbene, 645
Allyl chloride, 577
2-Allylcyclohexanone, 620
Allyl ethers, 779
Allylic carbanions, 144
Allylic cations, 270
  electronic structure of, 34
  formation of, 127, 800
  resonance in, 127
Allylic halides, coupling with Grignard reagents, 353

Allylic halides, reaction with acetylene, 649
Allylic halogenation, 535
Allylic radicals, 34, 154, 527
Allylic rearrangement (*see* Rearrangements, allylic)
Allyllithium, 475
Allylmagnesium bromide, 191
Allyloxyalkylquinolines, 834
Allyloxy imines, 833
Allylphenols, formation of, 454, 830
Allyl vinyl ethers, 833
Alpha effect on nucleophilicity, 290
Alternant hydrocarbons, electronic structure of, 46
  substitution of, 391, 498, 530
Alternating axis of symmetry, 74
Aluminum, 903
Aluminum anilides, 408
Aluminum aroxides, 408
Aluminum bromide, in Friedel-Crafts reactions, 407, 412
  in isomerization reactions, 433, 439
  reaction with propyl bromide, 795
Aluminum chloride, in acyloxylations, 426
  in addition, of aniline to benzonitrile, 673
    of halides to olefins, 615, 616
  in alkene acylation, 463
  in amidations, 416
  in aminations, 400
  in aromatic rearrangements, 428, 429
  in carboxylations, 420
  in Claisen rearrangement, 833
  in dealkylations, 433
  in dehalogenations, 439
  in ether cleavage, 344
  in ether formation, 317
  in formylations, 417, 419
  in Friedel-Crafts reactions, 407–415, 433
  in halogenations, 404
  in homologization of aldehydes, 811
  in Pechmann reaction, 423
  reaction, with arenes and HCl, 380
    with diethylbenzenes, 383
  in rearrangements of aromatic compounds, 434
  in reduction of alkyl halides, 348
  in sulfonylations, 403
  in sulfurizations, 402
Aluminum ethoxide, 910
Aluminum isopropoxide, 680, 681
Aluminum oxide, 753–756
Ambident nucleophiles, 298
Ambident substrates, 302
Amidals, 717
Amidation of aromatic rings, 416
Amides, acylation of, 340, 364
  addition to multiple bonds, 590, 660
  alcoholysis of, 323, 847
Amides, alkylation of, 340, 357
  cleavage of N-alkyl groups from, 315
  conversion, to anhydrides, 325, 327
    to imidates, 849
    to triazenes, 486
  dehydration of, 754, 777
  exchange, with acids, 325, 338
    with acyl halides, 335
    with amines, 339
  formation of, 315, 334–340, 416, 431, 483, 590, 606, 609, 660, 669, 691, 715, 725, 804, 809, 817, 819, 821, 848, 910 (*see also* 961)
  N-halogenation of, 487
  hydrolysis of, 313
  in Mannich reaction, 670
  N-nitration of, 486
  N-nitrosation of, 486
  protonation of, 221*n*.
  pyrolysis of, 757
  reaction, with aldehydes, 668
    with alkynyl ethers, 714
    with aromatic rings, 418
    with organometallic compounds, 363
    with phosphorus pentachloride, 684
    with sulfur tetrafluoride, 677
  rearrangement of, 816
  reduction of, 352, 895
Amidines, formation of, 591, 673
Aminals, 668, 672
Amination, of aromatic compounds, 400, 510
  of nitrogen heterocycles, 510
Amine oxides, cleavage of, 750, 761
  electronic structure of, 16
  formation of, 886
  optical activity of, 75
  reduction of, 901
Amines, acylation of, 414
  addition to multiple bonds, 589, 606
  alkylation of, 408, 411
  in aminoalkylation, 424
  in Arndt-Eistert synthesis, 809
  basicity of, 220, 228, 229
  cleavage of, 346
  in complex formation, 67, 69
  conversion, to N-cyanoamines, 346
    to imines, 883
    to nitriles, 866
    to quinolines, 423
    to quinones, 865
    to triazenes, 486
  in Cope reaction, 761
  coupling of, 549
  dehydrogenation of, 861
  diazonium coupling of, 399
  diazotization of, 290, 291, 305, 484
  in Favorskii rearrangement, 804
  formation of, 313, 331–334, 339, 340, 346,

Amines, formation of, 350–352, 355, 373, 400, 424, 430–432, 502–503, 510, 516, 519, 556, 589, 607, 656, 658, 668–670, 682, 683, 689, 725, 758–761, 776, 816–821, 825, 828, 848, 872, 883, 895, 897–903 (*see also* 962)
  formylation of, 417, 418, 420
  haloalkylation of, 424
  halogenation of, 403, 405, 487
  in hydrocarboxylation, 609
  hydroxylation of, 539
  introduction of diazonium group, 399
  in Mannich reaction, 670
  nitration of, 397, 486
  nitrosation of, 398, 486
  optical activity of, 75
  oxidation of, 855, 865, 884–886, 889
  in Passerini reaction, 726
  reaction, with acyl halides, 335, 766
    with aldehydes, 667
    with alkyl halides, 331
    with amides, 339
    with anhydrides, 336
    with aryl compounds, 502–503
    with carbon disulfide, 673
    with carboxylic acids, 336
    with carboxylic esters, 338
    with chloroform, 334
    with cyanide ion and aldehydes or ketones, 710
    with cyanohydrins, 332
    with diazo compounds, 333
    with epoxides, 334
    with isocyanates, 672
    with ketones, 667
      and sulfur, 910, 911
    with nitriles, 673
    with nitrogen heterocycles, 510
    with nitroso compounds, 908
    with sulfonyl halides, 374
  rearrangement of, 431
  reduction of, 350
  reductive alkylation of, 668
  sulfurization of, 403
  transamination, 333
o-Aminoacetophenone, 461
Amino acids, conversion to cyclic amides, 337
  formation of, 313, 331, 358, 462, 660, 670, 700, 710, 817, 902 (*see also* 963)
  reaction with trifluoroacetic anhydride, 336
Amino aldehydes, 484
Aminoalkylation, 424
Amino amides, 726
Amino azo compounds, 399, 400, 431
o-Aminobenzoic acid, 817
2-Amino-5-chlorothiophenol, 403
3-Amino-2,3-dimethyl-2-butanol, 799
1-Amino-7,7-dimethylnorbornane, 784
Amino esters, conversion to diazo compounds, 484
Amino esters, cyclization of, 338
  formation of, 845
  rearrangement of, 847
Amino ethers, formation of, 319
  reaction with Grignard reagents, 355
2-Amino-3-ethylpyridine, 510
Amino halides (*see* Haloamines)
Amino imides, formation of, 726
Amino ketones, conversion to diazo compounds, 484
  formation of, 333, 670, 815, 825
Amino ketoximes, 776
Amino mercaptans, formation of, 334, 403
3-Amino-4-methylsulfonic acid, 501
Aminophenols, 519, 539
β-(*o*-Aminophenyl)α,β-unsaturated ketones, 667
β-Amino-α,β-unsaturated ketones, 300
Ammonia, addition to multiple bonds, 589, 666
  in Arndt-Eistert synthesis, 809
  as basic solvent, 223
  basicity of, 220, 229
  bond angles of, 10, 12, 24
  in Mannich reaction, 670
  in nitrile formation, 676
  in Passerini reaction, 726
  reaction, with acyl halides, 335
    with aldehydes, 666
    with alkyl halides, 331
    with anhydrides, 336
    with aryl compounds, 502–503
    with carboxylic acids, 336
    with carboxylic esters, 338
    with cyanates, 673
    with cyanide ion and aldehydes or ketones, 710
    with cyanohydrins, 332
    with diazo compounds, 333
    with epoxides, 334
    with ketones, 666
      and sulfur, 910
    with nitriles, 673
    with ozonides, 871
    with sulfonyl halides, 374
  reductive alkylation of, 668
Ammonium chloride, 504
Ammonium dihydrogen phosphate, 676
Ammonium hydrogen sulfite, 501
Ammonium polysulfide, 910
Ammonium sulfide, 897
Amphoteric species, definition of, 217
tert-Amylbenzene, 434
tert-Amyl bromide, 741
tert-Amyl cation, 126, 785, 786
tert-Amyl chloride, 733
  formation of, 269
  reaction with cresol, 409
Anchimeric assistance, 263
  in elimination reactions, 733

Angelic acid, 449
Anhydride exchange, 324, 325
Anhydrides, in acylation of aromatic rings, 413–415
  in acylative decarboxylation, 480
  condensation with aldehydes, 698
  conversion, to acyl halides, 347
    to amides, 336
    to azides, 341
    to carboxylic acids, 309
    to esters, 320
    to imides, 340
    to peracids, 326
    to thiol acids and esters, 329
  exchange, with acids, 325, 480
    with acyl halides, 324
  formation of, 324, 325, 327, 545, 587, 823, 875, 902 (*see also* 963)
  halogenation of, 460
  reaction, with acetals, 464
    with aldehydes, 716
    with alkenes, 463
    with ketones, 364
    with nitric acid, 327
    with organometallic compounds, 363, 689
    with sulfur tetrafluoride, 678
  reduction of, 896, 897
  self-condensation, 365
Aniline, electronic structure of, 36
  formation of, 432, 492
  reaction, with aldehydes, 238
    with benzonitrile, 673
    with phenyl azide, 818
Anionic cleavage, 477–483
Anionotropic rearrangements, 781–790
Anisole, alkylation of, 411
  Birch reduction of, 597
  coupling of, 549
Annellation, 40
  in biphenylene, 51
  in indene and fluorene, 41
"Annual Reports," 947
"Annual Surveys of Organometallic Chemistry," 947
[4]Annulene, 48
  (*See also* Cyclobutadiene)
[6]Annulene, 48
[8]Annulene, 48
  (*See also* Cyclooctatetraene)
[10]Annulene, 48, 52, 54
[12]Annulene, 54
[14]Annulene, 53, 55
[16]Annulene, 53, 194
[18]Annulene, 52
  formation of, 549
  nmr spectrum, 194
[24]Annulene, 53, 194
[30]Annulene, 52, 54
Annulenes, 48, 52–55
Annulenes, formation of, 549
A nomenclature, 921, 928
Anthracene, in complex formation, 68
  in Diels-Alder reaction, 628
  formation of, 410
  free valence in, 56
  methylation of, 509
  oxidation of, 882
  photooxidation of, 621
  resonance in, 37
  resonance energy of, 39
Anthracene-9,10-epidioxide, 621
Anthraergostapentaene, 797
Anthranilic acid, 494
Anthraquinone, formation of, 882
  reduction of, 894
Anthrasteroid rearrangement, 797
9-Anthrol, 753
Anthrone, 894
β-(9-Anthryl)ethanol, 135
Anthrylethyl bridged cation, 135
β-(9-Anthryl)ethyl tosylate, 135
Antibonding orbitals (*see* Orbitals, antibonding)
Anti conformation, 103
Anti isomers, 95
Anti-Markovnikov addition, 577
  of amines, 591
  of bisulfite ions, 589
  of hydrogen bromide, 580
  of hydrogen sulfide, 588
  of RSH, 588
  of water, 600
Antimony pentachloride, in Friedel-Crafts reactions, 407
  reaction with aromatic rings, 405
Antimony pentafluoride, reaction, with alkyl fluorides, 126, 127
    with alcohols and FSO_3H, 126, 128
Antimony trichloride, in aryl rearrangements, 429
  in Friedel-Crafts reactions, 407
  reaction with alkyl halides, 342
Anti-periplanar conformation, 728–732, 759
Anti-Zaitsev elimination, 730, 739
  (*See also* Hofmann's rule)
A1 mechanism, 290, 310
Appearance potentials, 198
Aprotic solvents, 224
  effect on ambident nucleophiles, 300
  in elimination reactions, 745
  nucleophilicity in, 288, 295
  in S_E1 reactions, 447, 448
Arbuzov reaction, 705
Arenes, acylation of, 413–416
  acyloxylation of, 426, 546
  addition reactions with halogens, 611
  alkylation of, 406–412
  amidation of, 416

Arenes, amination of, 400
  arylation of, 412, 550–553
  carboxylation of, 420
  chlorination rates, 381–382
  condensation with aldehydes or ketones, 421–424
  conversion, to nitro compounds, 434
    to phenols, 426, 877
  coupling of, 549
  dealkylation of, 433
  in Diels-Alder reaction, 627
  formation of, 349, 350, 354, 406–413, 421, 433–436, 438–441, 478, 480, 505–509, 513, 550, 553, 555, 556, 608, 642, 709, 836, 859–862, 867 (*see also* 964)
  formylation of, 416–420
  haloalkylation of, 424
  halogenation of, 403
  halosulfonation of, 402
  hydroxylation of, 426
  introduction of diazonium group, 400
  in Jacobsen reaction, 436
  mass spectroscopy, 197
  metalation of, 469
  nitration of, 396
  nitration rates, 382
  nmr, 184
  oxidation of, 538, 875, 876, 880–882
  ozonolysis of, 872
  reaction, with carbenes, 466, 647
    with free radicals, 528
    with nitriles, 424–425
  reduction of, 597
  sulfonation of, 401
  sulfonylation of, 403
  sulfurization of, 403
Argon, 70
Arndt-Eistert synthesis, 809
Aromatic compounds in complexes, 66, 67, 69, 380–382
Aromatic duet, 49, 51
Aromaticity, 37–56
  definitions, 37
  determined by nmr, 193
Aromatic rings in nmr, 184, 193
Aromatic sextet, 29, 38–46
Aromatic substitution (*see* Electrophilic substitution; Free radical substitution; Nucleophilic substitution)
Aromatic systems, of eight electrons, 51–52
  of four electrons, 49–51
  of six electrons, 38–46
  of ten or more electrons, 52–54
  of two electrons, 49
Aromatization, 423, 859–862
1-Aroyl-2-aryl-1,2-dichloroethanes, 737
Arrhenius activation energy, 213
Arsines, 474, 476
4-Aryl-1-acetoxy-3-pentenes, 579
N-(β-Arylalkyl) amides, 422
β-(Arylamino)propionaldehydes, 423
Arylation, of active hydrogen compounds, 506
  of alcohols and phenols, 500
  of alkenes, 552
  of amines, 502
  of aromatic rings, 412, 524, 550–553, 555
  of aryl halides, 507
  of Grignard reagents, 506
  of mercaptans, 500
  of nitrogen heterocycles, 509
Aryl cations, structure of, 491
1-Aryl-2,2-dimethyl-1,3-butanediones, 847
β-Arylethyl compounds, 746
Aryl halides, addition to alkenes, 615
  in arylation, of aromatic rings, 413
    of enamines, 465
  conversion, to amines, 502
    to aryl ethers, 500
    to carboxylic esters, 507
    to nitriles, 506
    to sulfur compounds, 500
  coupling of, 507
    with alkyl halides, 354
  formation of, 403–406, 431, 438, 439, 476, 503–504, 512–513, 554, 559, 560 (*see also* 964)
  haloalkylation of, 424
  hydrolysis of, 499
  in Jacobsen reaction, 436
  nitration of, 388
  reaction, with acetylene and CO, 650
    with active hydrogen compounds, 506
    with halide ions, 503
    with metals, 475
    with organometallic compounds, 476, 506
  rearrangement of, 439, 440
  reduction of, 439
1-Aryl-4-methyl-1,3-pentanediones, 847
Aryl phosphates, formation of, 504
Aryl phosphites, reduction of, 505
Arylpropynoic acids, 584
Arylpyruvic acids, 700
Aryl sulfonates (*see* Sulfonic acid esters)
2-Arylthiophenes, 508
Arynes, 492–494
Ascaridole, 622
Aspartic acid, 73
Asymmetric atoms, 74, 75
Asymmetric carbanions, 148
Asymmetric carbons, 74
  in cyclic compounds, 98
Asymmetric centers, 81
  creation of, 81, 90
  more than one in a molecule, 87
Asymmetric reduction, 91
Asymmetric synthesis, 90–92, 603, 833
Atomic orbitals, 3–8
  linear combination of, 8

Atropine, 671
Atropisomers, definition of, 103
A2 mechanism, 290, 310
Autoxidation, 543
  of alcohols, 870
  of arene side chains, 877
  of boranes, 890
  of ketones, 870
  of phenols, 866
  of sulfur compounds, 885, 889
Axial bonds in six-membered rings, 105–107
1-Azabicyclo[4.4.0]decane, 861
1-Azabicyclo[4.4.0]dec-5-ene, 861
14-Azacyclohexacosanone, catena compound of, 906
Azenes, 162
Azepindiones, 820
Azide ion, in azidochlorination of alkenes, 614
  conversion to alkyl or acyl azides, 341
  effect on solvolysis reactions, 260–262
  reaction with alkenes and hydrogen peroxide, 623
Azides, conversion to amines, 502, 899–900
  in 1,3-dipolar addition, 623–625
  formation of, 341, 485, 614, 623, 818, 820 (*see also* 965)
  hydrolysis of, 499
  rearrangement of, 818
  reduction of, 899–900
  ring expansion of, 818
α-Azidopropionic acid, 85
Azines, formation of, 674
Aziridines, conversion to amino ethers, 319
  formation of, 332, 690, 722, 899 (*see also* 965)
  in nucleophilic substitution, 290, 302
  reduction of, 351
Azirines, 690, 816
Azlactones, formation of, 699
  conversion, to amino acids, 700, 902
    to pyruvic acids, 700
Azoamines, 438
Azobenzenes, 886
Azo compounds, in arylation reactions, 551
  formation of, 399, 431, 438, 441, 461, 555, 851, 867, 889, 901, 907–908 (*see also* 965)
  geometrical isomerism of, 95
  reduction of, 899–900, 902
  reductive alkylation of, 670
Azoxy compounds, in 1,3-dipolar addition, 624
  formation of, 886, 907, 908
  rearrangement of, 851
  reduction of, 900, 902
Azulenes, 44, 88
  formation of, 860
  formylation of, 418

$B_{AC}1$ mechanism, 310–313
$B_{AC}2$ mechanism, 310–314, 338
Baeyer test, 617
Baeyer-Villiger condensation, 411
Baeyer-Villiger rearrangement, 620, 822
Bakelite polymers, 422
Baker-Nathan effect, 57, 193
  and σ values, 243
Baker-Nathan order, in aromatic substitution, 386
    in nucleophilic substitution, 286
$B_{AL}1$ mechanism, 311–313
$B_{AL}2$ mechanism, 311–313
Bamford-Stevens reaction, 763
Banana bonds, in double bonds, 14
  in three- and four-membered rings, 117
  in triple bonds, 15
Barbaralanes, 843
Barbier-Wieland procedure, 875
Barbituric acid, 340, 547
Barium permanganate, 885
Barriers to rotation, 102, 196
  determination of, 182
Barton reaction, 850
Base catalysis, 226
  in aromatic nucleophilic substitution, 490
Bases, resolution of, 93
Base strength, 217–222
  determination of, 194
  effects of medium on, 229
  effects of structure on, 228
  table of, 219–221
Basicity, and leaving group ability, 290
  and nucleophilicity, 288
Basic nature of carbanions, 142
Basic solvents, 222
Basketane, 118
Bathochromic shifts, 172
Beckmann rearrangement, 784, 821
  abnormal, 777
Beilstein ("Handbuch der organischen Chemie"), 942–944, 952
Benedict's solution, 539
Bent bonds, in double bonds, 14
  in three- and four-membered rings, 117
  in triple bonds, 15
Benzaldehyde, asymmetric reduction of, 91
  condensation reactions of, 695, 697, 715
Benzaldehydes in Perkin reaction, 654
Benzamide, hydrolysis of, 277, 314
Benzcyclopropene, 121
Benzene, acylation of, 415
  addition reactions with halogens, 611
  alkylation of, 406, 408, 410, 411, 509
  carboxylation of, 420
  in complexes, 67, 69, 380–382
  cyanogenation of, 425
  in Diels-Alder reaction, 627
  electronic structure of, 28–31
  formation of, 433, 436, 480, 593, 642, 703, 859, 861

Benzene, formylation of, 417, 418
  free valence in, 56
  haloalkylation of, 424
  in nmr, 184
  oxidation of, 97, 875, 882
  ozonolysis of, 872
  reaction, with carbenes, 647
    with hydrogen halides, 380
    with maleic anhydride, 637
  reduction of, 597
  substitution rates, 394
  valence isomers of, 643
Benzenechromium tricarbonyl, 67
Benzenediazonium ion, bond distances in, 484
  coupling with naphthols, 379
Benzene-maleic anhydride photoadducts, 637
Benzene rings, orientation in, 382–393
  ubiquity of, 48
Benzhydryl chloride, 257
Benzhydryl *p*-toluenesulfinate, 305
Benzidine rearrangement, 828
Benzidines, 68, 828
Benzil-benzilic acid rearrangement, 803
Benzil bistosylhydrazone, 764
Benzilic acids, 803
Benzils, formation of, 507
  rearrangement of, 803
  reduction of, 803
Benznorbornadiene, 627
Benzoates in mixed Claisen condensations, 366
Benzoic acid, disproportionation of, 436
  electrolysis of, 558
Benzoin condensation, 714
Benzoins, formation of, 714, 803
Benzonitrile, reaction, with 2-allylcyclohexanone, 620
    with aniline, 673
  resonance in, 232
Benzophenone, condensation with diphenylmethane, 697
  conversion to phenyl benzoate, 823
  dimerization of, 175
  formation of, 480
  oxidation of amines, 883
  reaction with carbanions, 518
Benzophenone N-chloroimine, 822
Benzoquinones, 866, 882
3,4-Benzotricyclo[4.2.1.$0^{2,5}$]non-3-ene, 637
1-Benzoxy-1-phenyl-2-propylammonium chloride, 235
β-Benzoylacrylonitrile, 575
Benzoyl chloride, acylation of *tert*-butyltoluene, 433
  exchange with aluminum chloride, 415*n*.
Benzoyldiphenylethylenes, 604
Benzoylformic acid, 91
N-Benzoylnorephedrine, 235
4-Benzoyloxy-1,1-binaphthyl, 558
Benzoyl peroxide, in halogenations, 404
  reaction with aromatic rings, 426
Benzpinacol, 175
Benzpyridones, 834
Benzyl alcohol, formation of, 679, 756
  reaction with phosgene, 320
Benzylamines, formation of, 517
  reduction of, 351
Benzyl benzoates, 277
Benzyl bromide, reaction, with methoxide ion, 215
    with sodium naphthoxide, 300
Benzyl bromides, reaction with pyridine, 57
Benzyl carbanions, electronic structure of, 47
  stability of, 144
Benzyl cations, 128
  electronic structure of, 47
  rearrangement to tropylium ions, 43, 197
Benzyl chloride, conversion, to bibenzyl, 354
    to propylbenzene, 353
    to stilbene, 887–888
Benzyl ethyl ether, 755
Benzylic alcohols, 349
Benzylic halides, condensation with aldehydes and ketones, 701
  coupling with Grignard reagents, 353
  formation of, 424, 533, 536
Benzylic halogenation, 533, 536
Benzyl methyl ether, 215
Benzyl methyl ketone, 911
1-Benzyl-2-naphthol, 360
Benzyl 2-naphthyl ether, 300
Benzylphenols, 429
Benzylpyridinium ions, formation of, 57
  reaction with benzaldehyde, 697
Benzyl radical, 154
  electronic structure of, 47
Benzyltrimethylamine, 518
Benzyne mechanism, 492–494
  orientation in, 495, 497
Benzynes, 122, 492–494
  2 + 2 cycloaddition reactions of, 636, 637
  as dienophiles, 627, 628
  trapping of, 206
Betaines, 769, 811
  in Wittig reaction, 705–708
Biaryls, formation of, 412, 507, 524, 550–553, 555, 836
Bibenzyl, 354
Bicyclic compounds, naming of, 924
  rearrangement of, 795
  stereochemistry of, 100
Bicyclo[1.1.0]butane, 118, 119
  formation of, 354, 645, 646
Bicyclobutanone, 808
Bicyclo[4.4.0]dec-1,6-en-2-one, 121
trans-Bicyclo[3.2.0]heptane, 99
Bicyclo[2.2.0]hexadienes, 642

Bicyclo[2.1.1]hexane, 118
Bicyclo[3.1.0]hexane, 579
3-Bicyclo[3.1.0]hexanol, 140
Bicyclohexenyl, 627
3-Bicyclo[3.1.0]hexyl cation, 131, 140
3-Bicyclo[3.1.0]hexyl tosylate, 140
Bicyclo[4.3.0]nona-2,4-diene, 836
Bicyclo[4.3.0]nonane, 466
Bicyclo[3.3.1]nonan-9-one, 811
Bicyclo[3.3.0]octa-3,7-dien-2,6-dione, 45
Bicyclo[4.2.0]octa-2,4-diene, 842
Bicyclo[2.2.2]octan-2,6-dione, 144
Bicyclo[2.2.2]octane-1-carboxylic acid, 529
Bicyclo[2.2.2]octylmethyl tosylates, 286
Bicyclopropyls, 645
Bicyclo[2.2.0] system, 99
Bimolecular reduction, 903–904
Bi naming, 922
Binaphthyl, 412
Binaphthyls, optical activity of, 78
Binary number method for naming diastereomers, 89
Biochemical methods, for determining absolute configuration, 85
  of resolution, 93
Biphenyl, 412
Biphenyl-2,2′-bissulfonic acid, 78
Biphenylene, 50, 391*n.*
Biphenylenes, formation of, 508, 636
Biphenyls, optical activity of, 76, 83
  (*See also* Biaryls)
2,2′,5-Biphenyltricarboxylic acid, 877
Bipyrryls, 78
Birch reduction, 597
Bird-cage hydrocarbon, 118
Bisacetates, 618
Bis(*o*-alkylidineaminophenoxy)alkanes, 903
Bisamides, formation of, 668, 717, 726
Bischler-Napieralski reaction, 422
2,2-Bis(12-chlorododecyl)-4,6-pentacosamethylen-5-aminobenzdioxole, 906, 907
Bis(*p*-chlorophenyl)acetic acid, 304
4,5-Biscyanomethylcyclohexene, 709
Bisdecarboxylation, 879
Bisdehydro[12]annulene, 54
1,8-Bisdehydro[14]annulene, 55
2,2,N,N-Bisdodecamethylene-4,6-pentacosamethylen-5-aminobenzdioxole, 906
Bisethanoallenes, 646
Bis(*o*-iminomethylphenoxy)alkanes, 904
Bis-3-methyl-2-butylborane (*see* Disiamylborane)
Bis(3-methyl-2-butyl)-4-methyl-2-pentylborane, 600
Bismuth trimethyl, 153
2,2′-Bis(*o*-nitrophenyl)ethyl disulfide, 520
Bisperoxides, 872
Bisquaternary ammonium salts, 760
N,O-Bistrifluoroacetylhydroxylamine, 675
Bis(triphenylphosphonium) *o*-xylylide, 708
Bisuccinimidyl, 536
Bisulfite addition compounds, 589, 665
  reaction with hydrogen cyanide, 710
Bisulfite ions, addition to alkenes, 589
  in Bucherer reaction, 499, 502
  reaction, with epoxides, 330
    with multiple bonds, 589, 665
Boat conformation, 105, 106
  in transition state, 836
Bohr radius, 4, 5
Bond angles, 24
  of alkenes, 14*n.*
  of boron trifluoride, 12
  of cyclic amines, 120
  of cyclohexane, 105*n.*
  determination of, 181, 182
  in mercuric chloride, 11
  in methane, 12
  strained, 116–124
  in water and ammonia, 10, 12, 24
Bond distances, 21–24
  in benzene, 31
  in biphenylene, 51
  in butadiene, 32
  in cyclooctatetraene, 51
  determination of, 181, 182
  in fluoromethanes, 58
  in naphthalene, 39
  tables, 22, 23
Bond energies, 24–27
  determination of, 198
  in electronegativity scale, 17
  and resonance, 29
  table, 26
Bonding, coordinate covalent, 16
  covalent, 8–15
  delocalized, 28–37
  ionic, 18
  localized, 3–27
Bonding orbitals (*see* Orbitals, bonding)
Bond order, in benzene, 28, 29
  in butadiene, 32
  molecular orbital, 29
  valence bond, 28, 598
Boord reaction, 771
Borane, 599
Boranes, conversion to amines, 591
  coupling of, 556
  equilibrium with alkenes, 766
  formation of, 474, 599, 766, 814 (*see also* 966)
  hydrolysis of, 593, 594
  oxidation of, 889
  reaction, with alkynes, 767
    with carboxylic acids, 471
  rearrangement of, 456, 814
  reduction of, 593, 594

Borazoles, 38
Borderline region in nucleophilic substitution, 261
Bornane, 922
Bornyl chloride, 750
Bornyl systems, rearrangement of, 791
Boron, hybridization in, 11
Boron tribromide, 344
Boron trichloride, in ether cleavage, 344
  in Friedel-Crafts reactions, 407
  reaction with organozinc compounds, 474
Boron trifluoride, in acylations, 364, 464, 714
  in addition to multiple bonds, 585, 590
  in amide-amine exchange, 339
  in amine alkylation, 333
  bond angles in, 12
  in ester formation, 322
  in ether cleavage, 344
  in formylations, 418
  in Friedel-Crafts reactions, 379, 406, 408, 409
  in homologization of aldehydes, 811
  in hydroxylations, 426
  in reaction, between alkynyl ethers and aldehydes or ketones, 714
    with Grignard reagents, 474
    with nitriles, 660
  in rearrangement of ethylbenzene, 433
  in reduction of esters, 896
Boron trifluoride-hydrogen peroxide, 823
Bouveault-Blanc procedure, 680, 897
Bredt's rule, 122, 739, 751
Bridged bromonium ions, 265, 563, 565, 572
Bridged carbonium ions (*see* Nonclassical carbonium ions)
Bridged radicals, 571, 791
Bridged ring systems, naming of, 924
  stereochemistry of, 100
Bridgehead positions, carbanions at, 147
  carbonium ions at, 129
  double bonds at, 122, 739
  electrophilic substitution at, 444, 446
  free radical reactions at, 529
  free radicals at, 155
  nucleophilic substitution at, 254, 258
British Abstracts, 941
Bromination, of 1-acetamino-2-ethoxynaphthalene, 390
  of alkanes, 531, 532
  of alkylbenzenes, 381, 382, 533, 535
  of alkyl bromides, 525
  allylic, 535
  of aromatic rings, 403, 406, 611
  of butadiene, 572
  of cyclodecene, 121
  of cyclopropene, 117
  of cyclopropylbenzene, 387
  of double bonds, 101, 563, 565, 574, 579, 611
  of enynes, 575
Bromination, of toluene, 395
  of triple bonds, 565
Bromine, in complex formation, 69
  in haloform reaction, 482
  oxidation, of alcohols, 862, 865
    of aldehydes, 539, 541
  reaction, with alkenes and dinitrogen tetroxide, 614
    with amides, 817
    with silver carboxylates, 529, 559
    with sulfonylhydrazides, 374
  in rearrangement reactions, 792
  (*See also* Bromination)
Bromine atoms, 527, 528, 531, 533, 536
  reaction with alkenes, 571
Bromine chloride, addition to alkenes, 511
  reaction with aromatic rings, 406
N-Bromoacetamide reaction with isonitriles, 726
N-Bromo amides reaction with alkenes, 535, 611
o-Bromoanisole, 493
Bromobenzene, 439, 494
p-Bromobenzonitrile, 490
1-Bromobicyclo[3.3.1]nonan-9-one, 254
1-Bromobicyclo[2.2.2]octane, 529
2-Bromobutane, 579
3-Bromo-2-butanol, 264
Bromobutenes, formation of, 535
2-Bromo-2-butene, 449, 571
N-Bromo-*tert*-butylamine, 535
2-Bromocyclobutanone, 808
4-Bromo-*tert*-butylcyclohexane, 525
N-Bromocaprolactam, 535
Bromochlorination of alkenes, 611
1-Bromo-3-chlorocyclobutane, 354
1-Bromocyclohexene, 570
2-Bromo-2-cyclohexenol, 800
1-Bromo-3,3-dimethylbicyclo[2.2.2]octane, 254
1-Bromo-1,2-dimethylcyclohexane, 566
3-Bromo-2,3-dimethylpentane, 739
Bromo esters, formation of, 716
Bromoethane, 744, 750
  conversion to Grignard reagent, 150
  reaction, with ammonia, 331
    with lead-sodium, 476
    with toluene, 395, 409
Bromoethane-^{14}C, 412
Bromofluorination of alkenes, 611
Bromofluorobenzenes, 389
Bromoform, in alcohol dehydration, 755
  formation of, 482
  Raman spectrum of, 181
N-Bromohydantoins, 535
Bromohydrins, conversion to alkenes, 772
  formation of, 612
Bromomethane, conversion to Grignard reagent, 150

Bromomethane, formation of, 344
  hydrolysis of, 287
1-Bromo-2-morpholino-2-phenylpropiophenone, 813
Bromonium ions, 563, 565, 572
  in nucleophilic substitution, 265
1-Bromonorbornane, 738
Bromooctanes, 70
Bromo oximes, formation of, 536
2-Bromopentane, 742
Bromopentanes, formation of, 343
2-Bromo-1-phenylethane, 412
1-Bromopropane, 744
  formation of, 579
  rearrangement to 2-bromopropane, 795
2-Bromopropane, 744
  bond angles of, 24
  formation of, 795
  pyrolysis of, 750
  solvolysis of, isotope effect, 215
1-Bromopropene, 570
α-Bromopropionic acid, 85
1-Bromopropyne, 571
α-Bromostilbene, 728
α-Bromostyrene, 552
β-Bromostyrene, 712
N-Bromosuccinimide, in allylic bromination, 535–537
  in bromination, 533
  formation of, 487
  oxidation of alcohols, 863
  reaction, with aromatic rings, 404
    with carbonyl compounds, 459
Bromosulfuric acid, 402
p-Bromotoluene, 390
Bromotrichloromethane, addition to alkenes, 615
  in halogenations, 533
  reaction with alkenes, 649
Brönsted acid-base theory, 217
Brönsted catalysis equation, 226, 227, 238
Brosylates, definition of, 305
Brucine, 92
B-strain, 127, 234, 282
  in hexaphenylethane, 154
Bucherer reaction, 500, 503
Bullvalenes, 843
Bunte salts, 328–330, 373
1,2-Butadiene, 79
1,3-Butadiene, conversion, to cyclododecatriene, 641
    to cyclooctadiene, 641
  coupling of, 608
  2 + 2 cycloadditions of, 636, 640
  in Diels-Alder reaction, 626, 632
  electronic structure of, 31–33, 35
  reaction, with ethylene, 603
    with halogens, 572
1,3-Butadiene, reaction, with hydrogen chloride, 573
Butadienes, reaction, with carbenes, 644
    with nitrene, 645
Butane, conformations of, 103, 104
  formation of, 117, 164, 468, 469
2,3-Butanediol, 208
Butanedione, 879
1-Butanol-1-*d*, optical activity of, 74
Butanols, formation of, 91, 292, 350
Butanone, asymmetric reduction of, 91
  condensation with benzaldehyde, 695
  formation of, 811
  infrared spectrum of, 176
  oxidation of alcohols, 863
  ultraviolet spectrum of, 171
1-Butene, allylic bromination of, 535
  deuterogenation of, 594
  formation of, 450, 466, 602, 766
  hydrogenation of, 595
2-Butene, formation of, 729, 767
  reaction, with carbene, 160
    with permanganate, 208
Butenes, formation of, 165, 292, 738, 739, 751
Butenols, 139, 270
3-Buten-1-ol tosylate, 139
β-Butenolactones, 723
Butenolides, 625
Butenols, 272
tert-Butoxide ion, in double-bond reduction, 595
  in Oppenauer oxidation, 863
  reaction with active hydrogen compounds, 357
sec-Butyl acetate, 751
tert-Butyl acyl peroxides, 472
tert-Butyl alcohol, 734
n-Butylamine, 292, 911
Butylamines, basicity of, 230
4-*tert*-Butyl-2-aminocyclohexanols, 291
n-Butylbenzene, 861
tert-Butylbenzene, dipole moment of, 57
  exchange reactions of, 453
  formation of, 790
  nitration of, 388, 548
tert-Butylbenzoic acids, 229
tert-Butyl bromide, 744
  formation of, 531
  hydrolysis of, 287
  pyrolysis of, 750
tert-Butylcarbene, 466
tert-Butyl cation, 126
tert-Butyl chloride, 734
tert-Butyl chromate, 884
4-*tert*-Butylcyclohexanecarboxylic acid, 108
4-*tert*-Butylcyclohexanone, 291
4-*tert*-Butylcyclohexyl brosylate, 268
4-*tert*-Butylcyclohexytrimethylammonium hydroxide, 759

3-*tert*-Butylcyclopentanecarboxaldehyde, 291
tert-Butyldimethylsulfoxonium ions, 734
4-*tert*-Butyl-1,2-epoxycyclohexane, 291
tert-Butyl ethers, cleavage of, 755
  formation of, 316, 472, 545, 585, 612
tert-Butyl group used to "freeze" conformations, 108
tert-Butyl halides, solvolysis of, 256
tert-Butyl hypobromite, 533
tert-Butyl hypochlorite, addition to alkenes, 612
  in chlorinations, 533, 535, 538
  reaction, with aromatic rings, 404
    with isonitriles, 726
    with nitrogen compounds, 487
Butylidene, 165
n-Butyllithium, in metalation reactions, 469
  reaction, with carbenes, 165
    with halides and olefins, 649
sec-Butyllithium, 767
tert-Butyllithium, 149
sec-Butylmagnesium bromide, 444
tert-Butylmagnesium bromide, 689
n-Butylmercuric bromide, 449
sec-Butylmercuric bromide, 444, 446
Butyl nitrites, 292
tert-Butyl peracetate, 545
tert-Butyl perbenzoate, 545
tert-Butyl peresters, 526
sec-Butylphenols, 429
tert-Butyl radical, 791
tert-Butyltoluene, acylation of, 433
tert-Butyltoluenes, formation of, 388
2-Butyne, 646
Butyrophenone anion, 289

C-acylation versus O-acylation, 298
Cadiot-Chodkiewicz procedure, 550
Cadmium ions, in hydroxylation of alkynes, 583
  in rearrangements, 436
Cage compounds, 69, 70
Cahn-Ingold-Prelog system, 84, 87
Calcium chloride, 765
Calcium oxide, 765
C-alkylation versus O-alkylation, 298, 300, 301
Camphene, formation of, 763, 795
Camphenilone, 146
Camphenonic acid, 479
Camphor, 100
Cannizzaro reaction, 908
Canonical forms, 9, 28
  of enolate ions, 61
  in hyperconjugation, 56–59
  rules in drawing, 34
  stability of, 35
Caproic acid, 352
Carane, structure of, 922
α-Carbalkoxy aldehydes, formation of, 367
Carbalkoxylation of aryl iodides, 507
Carbamates, addition to multiple bonds, 590
  formation of, 335, 342, 483, 590, 663, 726, 817, 818 (*see also* 966)
  hydrolysis of, 313
Carbamic acids, 658
Carbamyl chloride, 420
Carbanion-Ei-ion pair spectrum, 748, 750
Carbanion mechanism of elimination, 735
Carbanions, 125, 142–152
  in addition to multiple bonds, 567
  in elimination reactions, 735
  formation from radicals, 157
  generation and fate, 151
  oxidation of, 544
  reaction, with alkyl halides, 357–362, 888
    with carbenes, 165
  in S_E1 reactions, 446
  stability of, 142–146
  structure of, 147, 446
Carbazole, 862
Carbenes, 125, 158–166
  addition, to ketenes, 625
    to multiple bonds, 643–649
  in Arndt-Eistert synthesis, 809
  in Bamford-Stevens reaction, 763
  in base-catalyzed ether cleavage, 756
  in cleavage of thionocarbonates, 768
  in decarboxylation of trihalo acids, 479
  formation of, 162, 164
  in formylation of aromatic rings, 419
  generation and fate, 162
  insertion reaction of, 466
  as intermediates in nucleophilic substitution, 293
  in olefin formation, 766
  reaction, with aromatic rings, 647
    with ketones, 811
  in Reimer-Tiemann reaction, 419
  stability, 158
  structure, 160, 161
Carbenoids, 643
α-Carbethoxybenzylmercuric halides, 451
Carbobenzoxy chloride, 320, 335
Carbodiimides, formation of, 718
  reaction with isothiocyanates, 719
  (*See also* Dicyclohexylcarbodiimide)
Carbonates, formation of, 319
  reaction with Grignard reagents, 688
Carbon, atomic, hybridization in, 12
    insertion reactions of, 466
    reaction with alkenes, 645
Carbon-carbon double bonds, addition reactions, 562–650, 711–713, 723–724
  electronic spectra of, 173
  electronic structure of, 13
  formation of, 727–776, 861, 887

- Carbon-carbon double bonds, geometrical isomerism of, 94–97
  - migration of, 449, 453, 586
  - as neighboring groups, 267
  - (*See also* Alkenes)
- Carbon-carbon triple bonds, addition reactions, 562–650
  - electronic structure of, 14
  - formation of, 727, 728, 731, 736, 753, 760, 765, 771, 774
  - migration of, 455
  - (*See also* Alkynes)
- Carbon dioxide, in carboxylation of aromatic rings, 420
  - in clathrate compounds, 70
  - reaction, with carbanions, 608
    - with Grignard reagents, 689
    - with sulfur tetrafluoride, 678
- Carbon disulfide, conversion to xanthates, 664, 757
  - reaction, with amines, 673
    - with Grignard reagents, 691
- Carbon isotope effects, 215
- Carbonium ions, 125–142
  - abstraction of hydride, 855
  - in addition to multiple bonds, 562, 715
  - in electrophilic aromatic substitution, 376, 379
  - in elimination reactions, 734, 748
  - formation of, 126–128, 140, 157, 772
  - in Friedel-Crafts alkylation, 410
  - generation and fate, 140
  - "hot," 291
  - hyperconjugation in, 58, 126
  - nonclassical, 130–140
  - rearrangements of, 782, 785
  - in S_N1 reactions, 256–258, 491
  - stability, 125
  - structure, 129
- Carbon-metal bonds, 142, 148
- Carbon monoxide, formation of, 304
  - in formylation of aromatic rings, 417
  - reaction, with acetylene and halides, 649
    - with alkenes, 608–610, 616
    - with alkyllithiums, 689
    - with ketones, 464
- Carbon-nitrogen double bonds, addition to, 651–654, 656–660, 663–665, 672, 682, 689–691, 709, 711, 718–719, 722, 724
  - in Diels-Alder reaction, 627, 628
  - electronic spectra of, 172
  - electronic structure of, 14
  - formation of, 866
  - isomerism of, 95
- Carbon-nitrogen triple bonds, addition to, 651–653, 660, 664, 673, 683–684, 691, 709, 715–720
  - in Diels-Alder reaction, 627
- Carbon-nitrogen triple bonds, electronic structure of, 15
  - formation of, 776–778, 866
  - (*See also* Nitriles)
- Carbon-oxygen double bonds, addition to, 651–726
  - in Diels-Alder reaction, 627, 628
  - electronic spectra of, 172
  - electronic structure of, 14
  - formation of, 778–779, 862–866
  - polarity of, 193
- Carbon suboxide, formation of, 754
  - reaction with ROH, 585
- Carbon-sulfur double bonds, addition to, 651–653, 664, 673, 691
  - isomerism of, 95
- Carbon tetrabromide, 181
- Carbon tetrachloride, addition to alkenes, 615
  - in carbonylation of aromatic rings, 421
  - in chlorinations, 533
  - formation of, 533
  - hydrolysis of, 304
  - reaction, with benzene, 406
    - with nitro compounds, 504
- Carbon tetrafluoride, 59, 678
- Carbonyl chloride fluoride, 504
- N,N'-Carbonyldiimidazole, in amide formation, 337
  - in ester formation, 322
- Carbonyl-forming cleavages, 477–481
- Carbonyl halides in carboxylation of aromatic rings, 420
- Carbonyl peak in the infrared, 179, 180
- 5-Carboxy-2-cyclohexenone, 650
- *o*-Carboxydiphenylamine, 414
- Carboxylation, of alkenes, 608
  - of aromatic rings, 420
  - with insertion of acetylene, 649
- Carboxylic acids, acidity of, 220, 228
  - in acylation of aromatic rings, 413–415
  - acylative decarboxylation of, 480
  - addition to multiple bonds, 586, 607
  - alkylation of, 357, 602
  - conversion, to acyl halides, 346
    - to amides, 336
    - to amines, 816, 819
    - to anhydrides, 324, 325, 327
    - to hydrazones, 461
    - to imides, 340
    - to ketenes, 754
    - to keto aldehydes, 657
    - to ketones, 370
    - to nitriles, 719, 778
    - to peroxides, 326
  - decarboxylation of, 370, 435, 477, 480
  - decarboxylative bromination of, 559
  - decarboxylative dimerization of, 557
  - esterification of, 320, 323, 324, 500
  - exchange, with acyl halides, 347

Carboxylic acids, exchange, with amides, 325, 338
    with anhydrides, 325, 480
    with esters, 325
  formation of, 304, 306, 308–315, 320, 323, 336, 339, 347, 357–358, 420–421, 462, 477, 478, 481–483, 514, 539–541, 582, 602, 608, 659-661, 689, 756, 776, 804, 823, 868, 870–872, 875–876, 883, 888, 908, 910 (*see also* 966)
  halogenation of, 460
  hydroxylation of, 511
  in Mannich reaction, 670
  naming of, 916
  oxidative decarboxylation of, 878–879
  in Passerini reaction, 725
  protonation of, 221*n*.
  reaction, with alkenes, 463
      and hydrogen peroxide, 619
    with alkyllithium compounds, 364
    with boranes, 593
    with cyclopropane, 579
    with esters, 325, 846
    with free radicals, 528
    with hydrazoic acid, 819
    with nitriles, 716
    with sulfur tetrafluoride, 677
  rearrangement of, 436
  reduction of, 352, 894
  in reduction of boranes, 471, 600
  resolution of, 92
  in Ritter reaction, 715
  (*See also* Dicarboxylic acids)
Carboxylic esters, acylation of, 364
  in acylation of aromatic rings, 407, 413
  acyloin condensation of, 904
  addition to olefins, 604, 606, 607
  alkylation of, 357
  in alkylation of aromatic rings, 407, 413
  arylation of, 506
  condensation with aldehydes or ketones, 696, 697
  conversion, to acyl halides, 347
    to amides, 338, 847
    to anhydrides, 324, 325, 327
    to ethers, 312
    to imides, 340
    to β-keto esters, 366–368
    to thiol acids and esters, 329
  coupling of, 549
  decarbalkoxylation of, 371
  exchange, with acids, 325
    with acyl halides, 347
  formation of, 306, 310, 315, 319–324, 357, 362, 363, 370, 426, 472, 481, 500, 507, 545, 559, 579, 583, 585–587, 606, 608, 609, 618, 664, 804, 809, 822, 865, 878, 883, 896, 910 (*see also* 967)
  hydrolysis of, 276–277, 309–313
Carboxylic esters, in Mannich reaction, 670
  protonation of, 221*n*.
  pyrolysis of, 747, 750–752, 756
  reaction, with alkynyl ethers, 714
    with amines, 338
    with carbanions, 369
    with free radicals, 528
    with ketones, 368, 696, 697
    with nitriles, 368
    with organometallic compounds, 363, 688
    with phosphines, 703
    with phosphoranes, 369
    with phosphorus pentachloride, 677
    with sulfur tetrafluoride, 678
    with zinc and α-halo esters, 688
  rearrangement of, 428, 845
  reduction of, 352, 505, 896
  tautomerism of, 60
  transesterification of, 322
  (*See also* Lactones; Unsaturated esters; etc.)
5-Carboxymethyl-2-cyclopentenone, 650
Caro's acid, 884–886
β-Carotene, 708
Catalysis, mechanistic information from, 206
Catalyst poisons, 351
Catechol, 866, 915
Catena compounds, 70, 905–906
Catenanes, 905–906
Cationotropic rearrangements, 781, 793, 798
Cellosolve, 319
Center of symmetry, 74
Ceric ammonium nitrate, 50
Cerium (IV), oxidation of alcohols with, 863
Chain reactions, 522
Chair-chair interconversion, 105, 192
Chair conformation, 105
  in a transition state, 836
Chapman rearrangement, 848
Charcoal in aromatization, 861
Charge-transfer complexes, 66–69, 174
Charge-transfer spectra and solvent polarity, 296
Charge types in nucleophilic substitution, 251, 255, 294–295
Chemical Abstracts, 939-941, 952–955
  indexes, 940–941
  indexing of names, 923
  journal abbreviations, 934, 935, 939, 946, 947, 954
  List of Periodicals, 954
  naming, 913
Chemical-Biological Activities, 941
Chemical literature, 932–955
Chemical patents, 936, 939
Chemical shift, 183, 187, 189, 190, 193
Chemical Titles, 937–939, 953
Chemisches Zentralblatt, 941, 954
Chichibabin reaction, 510
Chirality, 71

Chloral, 421, 713
Chloral hydrate, 665
N-Chlorimines, 776, 816
Chlorination, of 1-acetamido-2-ethoxynaphthalene, 390
  of aldehydes, 538
  of alkanes, 531, 532
  of alkenes and alkynes, 535, 567, 574, 611
  of aromatic rings, 381–382, 403, 406, 611
  of butadiene, 572
  of chloronitrobenzene, 389
  of isobutane, 791
  of toluene, 387
Chlorine, in clathrate compounds, 70
  in complex formation, 69
  in haloform reaction, 482
  in oxidation of isonitriles, 886
  reaction, with alkanes and SO_2, 546
    with hydrazides, 347
    with nitro compounds, 504
    with silver carboxylates, 559
  van der Waals radius, 123
  (*See also* Chlorination)
Chlorine atoms, 527, 528, 531, 533, 534
Chlorine fluoride, hybridization in, 195
Chloroacetylene, 279
β-Chloroacroleins, 774
β-Chloro acyl halides, formation of, 616
N-Chloro amides, 404
Chloroamine, reaction with boranes, 591
N-Chloroamines, addition to multiple bonds, 614
  reaction with aromatic rings, 400
Chloroamines, formation of, 614
4-Chloro-1-aminobutane, 332
Chloroanilines, 403, 497
1-Chloroapocamphane, 258
Chloro azides, formation of, 614
Chlorobenzene, condensation with chloral, 421
  electronic structure of, 34
  formylation of, 418
  hydrolysis of, 499
1-^{14}C-Chlorobenzene reaction with amide ions, 492
p-Chlorobenzhydryl chloride, 259
p-Chlorobenzoic acid, 206, 389
p-Chlorobenzonitrile, 206
1-Chloro-2-bromoethane, 565
1-Chlorobutane, formation of, 292
  conversion to butene, 765
1-Chloro-2-butene, 270
3-Chloro-1-butene, 270, 271
Chlorobutenes, formation of, 272
Chlorocarbene, 644, 647
1α-Chloro-5-cholesten-3β-ol, 89
Chlorocyclohexane, 106
2-Chlorocyclohexanone, 805
1-Chlorocyclopentene, 280
Chloro-2,3-dimethylbutanes, 531
3-Chloro-2,3-dimethyl-2-butanol, 799
1-Chloro-1,2-dimethylcyclopentane, 566
1-Chloro-3,3-dimethylpentane, 151
3-Chloro-2,6-dinitro-2′,6′-dicarboxybiphenyl, 77
Chloroethane, 150
1-(2-Chloroethylidene)-2,2,6-trimethylcyclohexane, 272
α-Chloro ethers, formation of, 676
2-Chloroethylamine, 332
(2-Chloroethyl)ethylenesulfonium ion, 289
1-Chloro-3-fluoropropane, 406
Chloroform, condensation with aldehydes and ketones, 697
  conversion to dichlorocarbene, 163, 304, 334, 419, 644, 722
  formation of, 533
  in formylation of aromatic rings, 419
  hydrogen bonding of, 65
  hydrolysis of, 304
  reaction, with amines, 334
    with benzene, 406
    with imines, 722
  in thiourea complexes, 70
Chloroformates, formation of, 319
  reaction with amines, 335
Chloroformamides, 335
Chlorofumaric acid, 731
Chlorohydrins, conversion to epoxides, 316
  formation of, 612
1-Chloro-2-iodopropane, 577
Chloromaleic acid, 731
Chloromethane, conversion to Grignard reagent, 150
  electronic spectrum of, 171
  formation of, 533
  quadrupole coupling constant, 195
N-Chloro-N-methylanilines, 405
Chloromethylation, 424
1-Chloro-3-methyl-2-butene, 274
3-Chloro-3-methyl-1-butene, 270, 578
4-Chloro-2-methyl-2-butene, 270, 578
1-Chloro-3-methylcyclobutane, 98
2-Chloro-2-methylpropanoyl chloride, 814
2-Chloronaphthalene, 648
m-Chloronitrobenzene, 389
p-Chloronitrobenzene, 516
α-Chloro nitro compounds, cleavage of, 762
2-Chloronorbornane, 529
1-Chloro-1-pentyllithium, 165
N-(*o*-Chlorophenyl)acetoacetamide, 507
4-Chloro-1-phenylbutane, 409
3-Chloro-1-phenyl-1-butene, 578
2-Chloro-1-phenylethane, 410
3-Chloro-1-phenylpropane, 406
Chloroplatinic acid, 592
3-Chloropropene, 573
3-Chloropyridine, 419
Chloroquinones, 278

Chlorosilanes, 474
α-Chlorostilbene, 553
Chlorosuccinic acid, 253
N-Chlorosuccinimide, reaction, with alkenes, 535
    with alkynes, 613
  oxidation of alcohols, 863
Chlorosulfenation, 547
Chlorosulfonation, 402, 546
Chlorosulfuric acid, reaction, with aromatic rings, 401, 402
    with formic acid, 417
Chlorotoluenes, 387
Chlorotrifluoroethylene, 574
Chlorotris(triphenylphosphine)rhodium, 560
Chloryl fluoride, 405, 458
7,9-Cholestadiene, 629
Cholestanones, 116
8-Cholestene, 592
3-Cholesteryl cation, 130
Chromatography for resolution, 93
Chromia-alumina catalysts, 861–862
Chromic acid (acid dichromate), 857*n.*
  oxidation, of alcohols, 862, 863, 870, 883
    of aldehydes, 539, 540
    of alkanes, 538
    of alkenes, 875
    of arene side chains, 876, 877, 880
    of arenes to quinones, 882
    of boranes, 600
    of diarylmethanes, 877
    of diols, 868, 870
    of hydroxylamines, 867
    of ketones, 870
    of phenols, 865, 866
    of trifluorotoluene, 304
Chromium chlorides, 555
Chromophores, 171
Chromous ion in reduction of double bonds, 592
Chromyl chloride, 880, 881
Chromyl trichloroacetate, 875
Chugaev reaction, 757
Cine substitution, 493, 499, 502, 515
Cinnamaldehyde, 589, 679
Cinnamic acid, 593, 641
Cinnamic acid derivatives, 552
Circular dichroism (cd), 114
Circularly polarized light, 72, 86, 92, 114
  (*See also* Polarized light)
Cis addition, to multiple bonds, 563–566, 569–571, 578
  of carbenes and carbenoids, 160, 646
  in Diels-Alder reaction, 629
  hydroboration, 600
  of hydrogen, 594
  of two OH groups, 616, 617
Cis elimination, 731–732, 735, 747–749, 752, 759, 761, 768, 769
Cis-trans isomerism, 94–100
Cis-trans isomerization, 175
Claisen condensation, 366, 696
Claisen rearrangement, 830–834
  abnormal, 831
Claisen-Schmidt reaction, 694, 695
Clathrate compounds, 69, 70
Clemmensen reaction, 891–894
^{13}C nmr, 189, 193
Cobalt bromide, 555
Cobalt chloride, in aryl rearrangements, 432
  in formylations, 418
  in halide coupling, 354
Cobalt fluoride, 611
Cobalt ions, catalysts, 545
Color, 169, 172
Column chromatography in resolution, 93
Common ion effect, 257, 295
Compendia, 942–944
Compound radicals in naming, 918
Condensations, acyloin, 904
  aldol, 672, 701
  base catalyzed, 691–709
    table, 693
  benzoin, 714
  Claisen, 366
  Darzen's, 700
  Dieckmann, 367
  Erlenmeyer, 699
  of esters and aldehydes or ketones, 696
  Knoevenagel, 697
  Perkin, 698
  as side reaction in Grignard addition, 686, 689
  Stobbe, 696
  Thorpe, 709
  Wittig, 702
Configurations, 71, 101, 103
  absolute, 82
  of cyclic ketones, 113
  determination of, 84, 86, 91, 97, 111, 174, 181, 191
  DL system, 83
  methods of determining, 113
  in molecules with more than one asymmetric center, 87
  RS system, 84
Conformational analysis, 101–116
Conformational effects on reactivity, 235
Conformational isomers, 102, 103
Conformational preference of groups in six-membered rings, 106
Conformations, in cyclic compounds, 104–109
  definition of, 101
  methods of determining, 109–116, 181, 192
  in open-chain systems, 102–104
Conformers, 102

Conjugate acid and base, definition of, 217
Conjugated systems, addition, of alkyl halides, 615
    of ammonia, 590
    of aryl halides, 615
    of carbamates, 590
    of N-haloamines, 614
    of hydrogen cyanide, 610, 710
    of hydrogen halides, 580
    of hypochlorites, 613
    of organometallic compounds, 604, 685
    of sulfur compounds, 588
  1,2-addition to, 568, 572
  1,4-addition to, 568, 572, 575–579, 653
  1,6 and 1,8-addition to, 568
  bis addition of bisulfite ions, 590
  2 + 2 cycloadditions, 637, 638
  Diels-Alder reactions, 626–636
  epoxidation of, 620
  formation of, 739, 751, 753, 760
  halogenation of, 612
  hydroboration of, 600
  Michael reaction, 604
  photooxidation of, 621
  reaction, with carbenes, 644, 646, 649
    with nitrenes, 645
    with olefins, 603, 626–636
  reduction of, 593, 594, 598
  in Wittig reaction, 703
Conjugation (*see under* Resonance)
Conjugative names, 922
Conrotatory motion, 839–841
Conservation of orbital symmetry, 633–636, 639, 641, 837*n.*, 839–841
Coordinate covalent bond, 16
Coordination compounds, stereochemistry of, 75, 76, 100
Cope reaction, 750, 761
Cope rearrangement, 641, 834–844
Copper, in addition of peroxides to alkenes, 587
  in alcohol dehydrogenation, 863
  in Arndt-Eistert synthesis, 809
  in decarboxylation, 435
  reaction, with aryl halides, 507
    with diazonium salts, 554
  reduction of quinones, 894
Copper acetylides, 507
Copper bronze, 888
Copper chromite, in alcohol dehydrogenation, 862, 863
  in hydrogenation, 349, 592, 680
  in reduction of esters, 896
Copper ions, in aromatic nucleophilic substitution, 502
  in hydration of alkynes, 583
  in Ullmann ether synthesis, 500
3-Coprostanone, 116
Corticosterone-21-acetate, 850
Cotton effect, 110–115
Coumarins, 423
Coupling constants, 187, 192, 193, 195
Coupling names, 917
Coupling reactions, alkyl, 548, 555
  of alkynes, 549
  aryl, 412, 507, 524, 550–553, 555
  of boranes, 556
  free radical, 548
  Kolbe reaction, 557
  of olefins, 607
  of organometallic compounds, 353–356, 362–364, 555
Cram's rule, 90, 651
Creatine, 180
o-Cresol, 389
p-Cresol, alkylation of, 409
  dipole moment, 19
  formylation of, 419
Crossed-Cannizzaro reaction, 702, 908
Crossover experiments, 428, 781
Crotylmercuric bromide, 449, 450
Crowded molecules, 122
Cubane, 118, 119, 925, 926
Cumene, autoxidation of, 544
  dipole moment of, 57
  formation of, 408
Cumene hydroperoxide, 544
Cumulenes, formation of, 771
  optical activity of, 79
Cumyl chlorides, solvolysis of, 236
Cupric benzoate, 546
Cupric carboxylates, 511
Cupric chloride, in arylations, 412
  in coupling reactions, 555
  in oxidation of hydrazine, 867
  reaction with carbonyl compounds, 459
Cupric ions, in acyloxylation, 545
  in alkyne coupling, 549
  in arylation of olefins, 552
  in oxidation of arenes, 877
Cuprous bromide, 647
  reaction with diazonium salts, 554
Cuprous chloride, 647
  in 1,4-addition of Grignard reagents, 604
  in addition of sulfonyl chlorides to alkenes, 613
  in alkyne dimerization, 603
  in formylations, 417
  in peroxide formation, 545
  in reaction, with aromatic rings, 405
    with diazonium salts, 554
Cuprous cyanide, reaction, with acyl halides, 370
    with aryl halides, 506
    with diazonium ions, 554
Cuprous ions, in acyloxylation, 545
  in alkyne coupling, 550

Cuprous ions, in biaryl formation, 554
  in diazonium cleavages, 554
  in nitration of diazonium salts, 554
Current Chemical Papers, 937
Current Contents Chemical Sciences, 937, 939
Curtius reaction, 783, 818
Cyanate ion, as ambident nucleophile, 298
  formation of, 886
  reaction with alkyl halides, 342
Cyanic acid, conversion to carbamates, 663
  in Passerini reaction, 726
  reaction, with ammonia and amines, 673
    with vinyl ethers, 591
Cyanide fusion, of aryl sulfonates, 506
Cyanide ion, alkylation of, 361
  as ambident nucleophile, 299, 300
  in benzoin condensation, 714
  as nucleophile, 499
  oxidation to cyanate ion, 886
  reaction, with aldehydes, 710
    with alkyl halides, 361
    with aromatic compounds, 425, 506
    with aromatic nitro compounds, 514
    with C═N compounds, 710
    with ketones, 710
α-Cyano acetals, formation of, 361
Cyanoacetic ester synthesis, 358
4-Cyano-4-acetoxycyclohexene, 632
1-Cyano-1-acetoxy-2-vinylcyclobutane, 632
Cyano acids, decarboxylation of, 477, 479
  formation of, 362
Cyanoamines, conversion to diazo compounds, 484
  formation of, 332, 670, 710, 711 (*see also* 968)
N-Cyanoamines, formation of, 346
1-Cyano-2-amino-3a,4,7,7a-tetrahydroindene, 709
1-Cyano-2-bromo-2-methylbutane, 526
Cyano enamines, formation of, 709
Cyano esters, formation of, 358, 369
Cyanoethylation, 568, 585*n.*, 588*n.*, 590*n.*
2-Cyanoethylcyclohexanone, 465
Cyanogenation of aromatic rings, 425
Cyanogen bromide, in amine cleavage, 346
  reaction with aromatic rings, 425
Cyanogen halides, 719
Cyanohydrins, conversion to cyanoamines, 332
  formation of, 710, 711
Cyano ketones, 361, 368, 370, 709
Cyanomethylation, 710
1-Cyano-2-methylbutane, 526
1-Cyano-2-methyl-1-butanol, 90
1-Cyanonaphthalene, 206
7-Cyano-7-trifluoromethyl-1,3,5-cycloheptatriene, 844
7-Cyano-7-trifluoromethylnorcaradiene, 844
1-Cyanovinyl acetate, 632
Cyclic compounds, geometrical isomerism of, 97–100
Cycloadditions, 618–649, 717–724
Cycloalkanes, in alkylation of aromatic rings, 407
  formation of, 360 (*see also* 969)
  strain in, 120
Cycloalkenes, formation of, 708 (*see also* 969)
Cycloalkyl groups as neighboring groups, 267
Cyclobutadiene, 48, 50
  in metal complexes, 50, 51, 67
Cyclobutane, conformation of, 108
  conversion to butane, 117
Cyclobutanes, cleavage of, 117, 838
  formation of, 633–641
  strain in, 117–120
Cyclobutanol, 139
Cyclobutenes, formation of, 165, 638, 640, 801
  rearrangement of, 838–841
Cyclobutenones, 636
Cyclobutylcarbinol, 799
Cyclobutylcarbinylamine, 799
Cyclobutyl chloride, 139
Cyclobutyl substrates, reactions of, 234
Cyclobutyl tosylate, 235
1,6-Cyclodecanedione, 869
Cyclodecapentaene (*see* [10] Annulene)
1,2,6,7-Cyclodecatetraene, 835
Cyclodecene, 121, 612
Cyclodehydration, 410
Cyclodehydrogenation, 861
1,5,9-Cyclododecatriene, 641
1,4-Cycloheptadienes, 835
Cycloheptatrienes, 43, 647, 836
Cycloheptatrienone, 44
Cycloheptatrienyl anion, 43, 52
Cycloheptatrienyl cation, 43
Cyclohexadienes, formation of, 597–599, 626, 835, 840
  reaction with diazonium ions, 514
Cyclohexadienones, rearrangement of, 802
  tautomerism of, 61
1,14-Cyclohexaeicosanedione, 557
Cyclohexane, bond angles in, 105*n.*
  in thiourea complexes, 70
1,4-Cyclohexanediol, 106
1,3-Cyclohexanedione, 145
Cyclohexanes, aromatization of, 859
  conformations of, 104–108, 192
  formation of, 597, 599, 861
1,2,3-Cyclohexanetriol, 99
Cyclohexanol, 865
Cyclohexanone, electronic spectrum of, 172
  oxidation of alcohols, 863
  oxidative cleavage of, 870, 871
Cyclohexanone oxime tosylate, 822
Cyclohexanones, formation of, 597, 800
  in Wittig reaction, 704
Cyclohexatriacontadodecayne, 550
Cyclohexene, addition of NOCl, 614
  autoxidation of, 544

Cyclohexene, disproportionation of, 861
  epoxidation of, 620
  as reducing agent, 593
Cyclohexene oxide, 99
Cyclohexenes, addition reactions of, 579
  formation of, 598, 626, 837
Cyclohexenones, 586
2-Cyclohexenyl hydroperoxide, 544
N-(1-Cyclohexenyl)pyrrolidine, 465
1-Cyclohexyl-3-methyl-1,3-butadiene, 841
1,2-Cyclononadiene, 122
3,5-Cyclononadienyltrimethylammonium ion, 836
Cyclononatetraenyl anion, 54
Cyclononylamine hydrobromide, 120
Cyclononyne, 122
1,3,7,9,13,15-Cyclooctadecahexayne, 549
1,3-Cyclooctadiene, 838
1,5-Cyclooctadiene, 641, 835, 837
1,15-Cyclooctaeicosanedione, 557
Cyclooctanediols, 848
Cyclooctanol, 543
Cyclooctatetraene, 48, 51
  formation of, 642
  in metal complexes, 67
  oxidation of, 190
Cyclooctatetraene oxide, 190
Cyclooctatetraenyl dianion, 54
1,3,5-Cyclooctatriene, 842
Cyclooctene, geometrical isomerism of, 96
trans-Cyclooctene, optical activity of, 80
  resolution of, 93
Cyclooctene oxide, 848
Cyclooctyne, 122
Cyclopentadiene, 627, 629
Cyclopentadienes, acidity of, 41, 43, 220
  alkylation of, 358
  condensation with aldehydes or ketones, 697, 698
  formation of, 861
Cyclopentadienone, 42, 44, 627*n*.
Cyclopentadienyl anion, 50
  aromaticity of, 41, 43
  in ylides, 42
Cyclopentadienyl cation, 50
π-Cyclopentadienyl-π-cycloheptatrienyl vanadium, 44
Cyclopentadienylides, 42
Cyclopentadienyl sodium conversion to metallocenes, 474
Cyclopentanecarboxylic acid, 871
Cyclopentanecarboxylic esters, 805
Cyclopentanes, conformation of, 109
  dehydrogenation of, 861
Cyclopentanol, 799
Cyclopentene, in Diels-Alder reaction, 633
  formation of, 645, 799, 837
Cyclopentenones, 586
Cyclopentylamine, 799
Cyclopentyne, 280
Cyclopropane, cleavage of, 801
  reaction with aromatic rings, 407
Cyclopropanecarboxylic acid, 808
Cyclopropanes, bonding in, 117
  formation of, 160, 268, 354, 356, 643
  ring opening reactions, 117, 579
  strain in, 117–120
Cyclopropanones, in Favorskii rearrangement, 805–808
  formation of, 644
Cyclopropenes, formation of, 646
  stability of, 121
Cyclopropenones, 49, 646
2-Cyclopropenylacetaldehyde, 833
Cyclopropenyl anion, 49, 50
Cyclopropenyl cation, 49, 50, 129
Cyclopropenyl radical, 49
2-Cyclopropenyl vinyl ether, 833
1-Cyclopropyl-1-arylethylenes, 579
Cyclopropylbenzene, 387
Cyclopropyl carbanions, 143, 145
Cyclopropylcarbenes, 165, 801
Cyclopropylcarbinylbenzyldimethylammonium ion, 517
(Cyclopropylcarbinyl)methyl-*o*-xylylamine, 517
Cyclopropyl cations, cleavage of, 800
Cyclopropylcyclopropenes, 646
Cyclopropyl halides, solvolysis of, 286
Cyclopropylidenes, 161, 165, 644
Cyclopropylmethanol, 139
(Cyclopropylmethyl)amine, 139
Cyclopropylmethyl cation, 128, 130, 139
Cyclopropylmethyl chloride, 139
2-Cyclopropyl-2-propyl cation, 128, 129
Cyclopropyl substrates, S_N1 reactions of, 234
Cyclopropyl-*o*-tolylcarbinyldimethylamine, 517
Cyclopropyl tosylate, 235
Cyclotetraeicosaoctayne, 550
Cyclotetratriacontane, 905, 906
Cyclotriacontadecayne, 550
Cysteine, 93

D (dissociation energy), 24, 155
Dakin reaction, 878
Darzen's condensation, 693, 700
DDT, formation of, 421
  naming of, 912
  reaction with hydroxide, 304
Deactivating groups, in electrophilic aromatic substitution, 382, 385–387, 389
  in nucleophilic aromatic substitution, 495, 496
Dealkylation of aromatic rings, 433
2,8-Decadien-4,6-diyne, 594
Decafluorocyclohexanes, 611
Decalin, 99, 544
Decalin-9,10-diol, 869

Decalin hydroperoxide, 544
Decalones, equilibration of, 458
Decarbonylation, of aldehydes, 435, 560, 790–792
  of carboxylic acids and esters, 314, 347
Decarboxylation, 358, 365
  of aliphatic acids, 477
  of aromatic acids, 435
  with concomitant acylation, 480
  of β-hydroxy acids, 699
  ketonic, 370
  oxidative, 878, 879
Decarboxylative dimerization, 557
Decarboxylative halogenation, 559
2,4,6,8-Decatetraene, 594
Decene, isomerization of, 456
  reaction with boranes, 766
Decomposition of radicals, 156, 157
Decoupling in nmr, 187
Decyanoethylation, 568*n*.
Degenerate Cope rearrangement, 842, 843
Dehalocarboxylation, 774
Dehalogenation, of aryl halides, 439
  of 1,2-dihalides, 770
Dehydration, of alcohols, 317, 753–755
  of amides, 754, 777
  of carboxylic acids, 325, 754
  of glycerol, 423
  of oximes, 776
Dehydroabietic acid, 921
Dehydro[14]annulene, 53
9,10-Dehydrodianthracene, 37
Dehydroergosterol, 797
Dehydrogenation, 859–867
Dehydrohalogenation, 765, 766
  free radical, 751
  with lithium chloride, 745
  pyrolytic, 750
Dehydro names, 922
Delta value in nmr, definition of, 185
Demerol, 808
Demyanov rearrangement, 800
Deoxybenzoin, structure, 921
Deoxycholic acid, 70, 93
Deoxy names, 922
Deshielding in nmr, 185, 193
Desulfonation of arenesulfonic acids, 439
Desulfurization, 556
Deuteration, of alkanes and alkenes, 452, 594
  of aromatic rings, 396
  at enolizable hydrogens, 458
Deuterioaniline, 429
Deuterium bromide, 566
Deuterium compounds, naming of, 930
Deuterium hydrogen bonding, 65
Deuterium isotope effects, 213–216
Deuterium sulfate, 567
Deuterogenation of alkenes, 594
Dewar benzene, 643
Dewar structures, 28
Dextro (+) rotation, 72
1,3-Diacetoxycyclohexane, 579
N,N-Diacyl amides, formation of, 335
Diacyl disulfides, formation of, 889
Dialdehydes, formation of, 464, 875
(*p*-Dialkylaminophenyl)carbinols, 438
3,3-Dialkyl-3*H*-indoles, 844
Dialkylmagnesium compounds, structure of, 149
Dialkylmercury compounds conversion to alkylmercuric chlorides, 471
α-Dialkylsulfonium carboxylic acids, 477
Dialkylvinylidinecarbenes, 161
Diamines, oxidation of, 876
Diaminobiaryls, formation of, 828
1,6-Diaminocyclodecane dihydrochloride, 120
2,4-Diaminodiaryl ethers, 505
2,6-Diaminospiro[3.3]heptane, 79
2,4-Diaminotoluene, 501
1,2-Diaroxy compounds, formation of, 824
Diarylacetylenes, formation of, 811
1,1-Diarylethanes, formation of, 407
1,1-Diaryl-2-haloethylenes, 811
3,3-Diaryl-2-halopropenoic acids, 813
Diarylhydrazines, rearrangement of, 828
Diaryl ketones, cyclization of, 410
Diarylmethanes, oxidation of, 876, 877
Diarylmethyl halides, solvolysis of, 256
Diastereomers, definitions of, 87, 98
  properties of, 87
  separation of, 92
Diazides, formation of, 623
Diazirines, 164
Diazo anhydrides, 551
Diazo compounds, in Arndt-Eistert synthesis, 809
  in Bamford-Stevens reaction, 763
  conversion to ethers, 317
  in 1,3-dipolar addition, 624
  formation of, 370, 485, 486, 780, 867 (*see also* 969)
  protonation of, 291
  reaction, with aldehydes and ketones, 721, 811
    with amides, 340
    with amines, 333
    with carboxylic acids, 324
    with sulfur, 722
Diazocyclononane, 466
Diazohydroxides, 293
Diazo ketones, in Arndt-Eistert synthesis, 809
  conversion, to α-halo ketones, 345
    to α-keto ethers, 317
  formation of, 370, 867
  hydrolysis of, 306
  reaction, with carboxylic acids, 324
    with ketenes, 625

Diazo ketones, reaction, with triphenylphosphine, 657
  reduction to methyl ketones, 346
Diazomethane, in Arndt-Eistert synthesis, 809
  in carbene formation, 161, 164, 466, 468
  formation of, 780
  in methylation, of alcohols and phenols, 317
    of amines, 333
    of carboxylic acids, 324
  reaction, with acyl halides, 370
    with aldehydes, 721, 810
    with aromatic rings, 647
    with iminium ions, 723
    with ketones, 721, 810
Diazomethyl triphenylmethyl ketone, 810
Diazonium coupling, aliphatic, 460
  aromatic, 399
Diazonium fluoborates, 513
Diazonium group, in activation of aromatic nucleophilic substitution, 495
  direct introduction of, 399
Diazonium ions, in arylation, of arenes, 550
    of olefins, 552
  in Bamford-Stevens reaction, 763
  conversion, to bromides, 554
    to chlorides, 554
    to fluorides, 513
    to iodides, 512
    to nitriles, 554
    to nitro compounds, 554
    to olefins, 762
    to phenols, 512
  coupling, with aliphatic compounds, 460
    with aromatic rings, 393, 399
  cyclization of, 551
  dimerization of, 555
  formation of, 290, 291, 305, 306, 399, 484
  migration of, 431
  in nucleophilic aliphatic substitution, 290
  reaction, with alkenes, 615, 876
    with (*p*-dialkylaminophenyl)carbinols, 438
    with metal aryls, 441
    with nucleophiles, 491
    with sulfur compounds, 512
  rearrangement of, 796
  reduction of, 513, 899–900
  stability of, 484
Diazosulfides, formation of, 512
Diazotization, 484
  of alkylamines, 305
  of amides, 314
  of cyclic amines, 799–800
  of (cyclopropylmethyl)amine, 139
Dibenzocarane, 163
Dibenzocyclooctatetraene, 708
Dibenzodioxa cyclic compounds, 904
Dibenzodioxadiaza cyclic compounds, 903
14*H*-Dibenzo[*a*,*h*]phenothiazine, 469
Dibenzyl ketone, 665
Dibiphenylylhydrazine, 828
Diborane, in borane rearrangements, 814
  reaction with multiple bonds, 599
  reduction, of aldehydes and ketones, 680
    of amides, 895
    of azo compounds, 902
    of carboxylic acids, 895
    of nitriles, 683
    of nitro compounds, 898
    of oximes, 683
    selectivity of reductions, 890–892
Diboranes, formation of, 600
Dibromobenzene, 439
6,6-Dibromobicyclo[3.1.0]hexane, 800
2,3-Dibromobutane, 729
  formation of, 264, 571
1,4-Dibromobutene, 572
3,4-Dibromo-*tert*-butylcyclohexane, 525
Dibromocarbene, 644
1,6-Dibromocyclodecane, 121, 612
2,2-Dibromocyclodecanone, 121
1,2-Dibromocyclohexane, 570
1,4-Dibromocyclohexane, 106
1,2-Dibromo-1,2-diphenylethane, 728
1,2-Dibromoethane, 104, 110, 565
2,3-Dibromofumaric acid, 565
1,12-Dibromo-5-methyldodecane, 74
1,3-Dibromopropane, 117, 354
1,2-Dibromopropene, 101
2,3-Dibromosuccinic acid, 101, 565
1,2-Dibromo-1,2,3,4-tetrachloroethane, 535
Dibromotrichloropropanes, formation of, 792
2,6-Di-*tert*-butyl-4-alkylphenols, 301
2,6-Di-*tert*-butylanisole, 301
1,2-Di-*tert*-butylbenzene, 123
2,3-Di-*tert*-butylbutadiene, 37
2,6-Di-*tert*-butyl-4,4-diethylcyclohexa-2,5-dienone, 301
1,2-Di-*tert*-butylethylene, 567
2,2-Di-*tert*-butylethyltrimethylamine, 760
Dibutyl fumarate, 70
Di-*tert*-butyl glutarates, 696
Dibutyl maleate, 70
Di-*sec*-butylmercury, 444, 445
2,6-Di-*tert*-butyl-6-methylcyclohexa-2,4-dienone, 301
Di-*tert*-butyl peroxide, in alkyloxylation, 545
  in decarbonylation, 560
  reaction with aldehydes, 790
2,6-Di-*tert*-butylphenetole, 301
2,6-Di-*tert*-butylphenoxide ion, 300
2,6-Di-*tert*-butylpyridine, 124, 228
Dicarbanions as ambident nucleophiles, 299
Dicarbenes, 161
Dicarboxyacetylene, 565, 731
Dicarboxylic acids, bisdecarboxylation of, 879
  conversion to cyclic anhydrides, 325

Dicarboxylic acids, cyclization of, 371
  formation of, 357–358, 416, 608, 870
  mono esters, formation of, 320, 323, 664
1,1-Dicarboxy-4-phenylbutadiene, 641
gem-Dichlorides, formation of, 677
Dichloroacetylene, 736
N,N-Dichloroamines, 815
N,N-Dichloroaniline, 431
2,4-Dichloroaniline, 431
4,4′-Dichloroazobenzene-2,2′-dicarboxamide, 516
o-Dichlorobenzene, 123
Dichlorobenzenes, isomerization of, 439
  reaction with amide ions, 497
3,4-Dichlorobicyclo[3.2.1]oct-2-ene, 648
1,1-Dichloro-2,2-bis(*p*-chorophenyl)ethylene, 304
1,4-Dichlorobutene, 572
Dichlorocarbene, 161, 644, 648
  formation of, 163
  in formylation of aromatic rings, 419
  in hydrolysis of chloroform, 304
  in isonitrile formation, 334
  reaction with imines, 723
1,4-Dichlorocyclohexane, 106
7,8-Dichloro-2,3;5,6-dibenzobicyclo[2.2.2] octane, 731, 732
2,2-Dichloro-3,3-difluorocyclobutane compounds, 639
1,1-Dichloro-1a,6a-dihydrocycloprop[*a*]indene, 648
1,2-Dichloroethane, 103
Dichloroethylenes, 279, 280
2,5-Dichlorohexane, 410
Dichloromethane, formation of, 533
  hydrolysis of, 304
  reaction, with benzene, 406
    with olefins, 649
4-Dichloromethyl-4-methyl-2,5-cyclohexadienone, 419
Dichloromethyl methyl ether, 419
Dichloronitrobenzenes, 389
2,3-Dichloro-1-propanol, 577
3,3-Dichloropropene, 573
3,3-Dichlorotricyclo[3.2.1.0^{2,4}]octane, 648
Dicobalt octacarbonyl, in addition of HCN to alkenes, 610
  in hydroformylation, 609
  in olefin trimerization, 642
"Dictionary of Organic Compounds," 944
Dicyanocarbene, 647
Dicyano compounds, conversion to imidates, 673
  formation of, 357, 876 (*see also* 970)
  reduction of, 683*n*.
Dicyanocyclobutane, 638
Dicyanonorcaradiene, 647
Dicyclohexylamine, 862
Dicyclohexylcarbodiimide, in formation, of amides, 337
    of esters, 321
    of ethers, 318
    of peroxides, 326
  in oxidation of alcohols, 882
Dicyclohexylurea, 321
Dicyclopropylmethyl cation, 128
Dieckmann condensation, 367
Dielectric constants of solvents, 224
Diels-Alder adducts, cleavage of, 631, 634
Diels-Alder reaction, 626–636
  with cyclobutadiene, 51
  with cyclopropanones, 806
  mechanism of, 630–633
  with oxygen, 622
Dienes, conversion to carbonium ions, 127
  Diels-Alder reactions of, 626–636
  formation of, 558, 760, 834–841
  reaction, with carboxylate ions, 558
    with diazonium ions, 460
  rearrangement of, 834–841
Dienone-phenol rearrangement, 802
Dienophiles, in Diels-Alder reaction, 626–636
  in 1,3-dipolar addition, 625
  in ene synthesis, 603
Diethers, rearrangement of, 799
Diethyl 2-acetyl-3-pentendioate, 606
Diethylamine, 271, 590
Diethylbenzenes, 383, 433
Diethyl α,α′-Diacetylsuccinate, 888
Diethylene glycol, 319
Diethylferrocene, 435
Diethyl fumarate, 70
Diethylmagnesium, 150, 151
Diethyl maleate, 70
Diethylmercury, 151
Diethylpropenylammonium ion, 271
Diethyl succinate, 696
Diethyl tetratriacontanedioic acid, 905, 906
Diffusion controlled reactions, 203
gem-Difluorides, formation of, 677
Difluoroamine, 350
cis-Difluorobis(ethylenediamine)cobalt (III) ion, 76
Difluorocarbene, 158*n*., 644
1,1-Difluoro-2,2-dichloroethylene, 639
Difluorodimethylcyclohexadienones, 405
Difluoroethanes, 611
α,α-Difluoro ethers, 678
1,1-Difluoroethylene, 636
Difluoromethane, 59
1,8-Difluorooctane, 558
Digonal hybridization, 11
Dihalides, in alkylation of aromatic rings, 406
  conversion, to acetals, 316
    to aldehydes or ketones, 303
    to alkenes, 770

Dihalides, conversion, to alkynes, 765
  cyclization with sulfide ion, 329
  formation of, 348, 532, 580, 610, 677, 817 (*see also* 970)
  reaction with active hydrogen compounds, 360
  reduction of, 348
Dihalo aldehydes, 612
1,1-Dihalo alkenes, 766
Dihalocarbenes, 643, 644, 647
Dihalocyclopropanes, 644
Dihalocyclopropenes, 646
Dihalo ketones, 612, 613, 807
9,10-Dihydroanthracene-9,10-diol, 753
Dihydroisoquinolines, 422
Dihydropyran, 755
Dihydropyridines, formation of, 683
Dihydropyrrole, 645
Dihydroquinolines, 423
Dihydrotestosterone, 721
2,2′-Diidobiphenyl, 508
Diimide in reduction of multiple bonds, 596, 680
4,6-Diiodo-1,3-dimethylbenzene, 439
Diiodomethane, 648
Diisobutylaluminum hydride, 352, 684
Diisopropylacetylene, 642
Diisopropyl ether, 864
Diisopropylneopentylcarbinol, 480, 686
Diketene, 636, 723
α-Diketone oximes, 776
1,2-Diketones, cleavage of, 868
  conversion to anhydrides, 823
  formation of, 872, 880
  reaction with hydrazines, 674
  rearrangement of, 803
  reduction of, 894
1,3-Diketones, ambident nucleophiles from, 298
  basic cleavage of, 481
  Clemmensen reduction of, 893
  conversion to triketones, 369
  formation of, 357, 364–366, 368, 465, 482
  reaction with hydrazines, 674
  reduction of, 680
1,4-Diketones, conversion to furans, 662
  dehydrogenation of, 861
  formation of, 307
Diketopiperazines, 337
1,4-Dimesityl-2,3-benzofuran, 632
Dimethoxycarbene, 159
Dimethoxyphenol, 405
Dimethylamine, 671
p-Dimethylaminobenzaldehyde, 715
4-Dimethylamino-2,4-dimethyl-2-chloropentane, 733
4-Dimethylamino-2-methyl-2-chlorobutane, 733
Dimethylaminophenylpentenes, 826
4-Dimethylamino-2,3,3-trimethyl-2-chlorobutane, 733
Dimethylanilines, 432
2,3-Dimethylbenzyldimethylamine, 518
1,3-Dimethylbicyclobutane, 646
5,5-Dimethylbicyclo[2.1.1]hexane, 118
2,6-Dimethyl-4-bromobenzonitrile, 490
2,3-Dimethylbutane, 531, 602
Dimethyl-2-butene, 873
2,4-Dimethyl-2-chloropentane, 733
3,4-Dimethylcyclobutene, 838–841
1,2-Dimethylcyclohexanecarboxylic acid, 807
1,2-Dimethylcyclohexanes, 106
1,2-Dimethylcyclohexanol, 566
1,2-Dimethylcyclohexene, 565, 566
1,3-Dimethyl-1,3-cyclopentadiene, 127
1,3-Dimethylcyclopentane, 98
1,2-Dimethylcyclopentene, 566
Dimethylcyclopropanes, 160, 466, 467
15,16-Dimethyldihydropyrene, 53
1,2-Dimethylenecyclobutanes, 636
Dimethyl ether, 24, 759
1,1-Dimethylethylene oxide, 811
1,1′-Dimethylferrocene-2-carboxylic acid, 80
Dimethylformamide, as aprotic solvent, 224
  formation of, 324
  reaction with acyl halides, 335
Dimethylformamide acetals, 324
Dimethylfulvene, 697
3,4-Dimethyl-1,5-hexadiene, 836
Dimethylmagnesium, 150
2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, 75
3,5-Dimethyl-4-nitrobromobenzene, 490
7,7-Dimethyl-1-norbornanecarboxamide, 784
2,6-Dimethyl-2,6-octadiene, 603
2,7-Dimethyl-2,4,6-octatrienedial, 708
Dimethyloxosulfonium methylide, reaction,
    with aldehydes and ketones, 721
  with alkenes, 649
  with nitro compounds, 509
3,3-Dimethylpentanal, 790
4,4-Dimethylpentanol, 542
2,3-Dimethyl-2-pentene, 739
3,4-Dimethyl-2-pentene, 739
Dimethyl-1-phenylethylsulfonium chloride, 255
(1,2-Dimethylpropyl)dimethylsulfonium ions, 739, 740
2-(1,2-Dimethylpropyl)-4-methylphenol, 409
2,6-Dimethylpyridine, 124
1,2-Dimethylstilbenes, 191
Dimethyl sulfide, 871
Dimethylsulfonium methylide reaction with aldehydes and ketones, 721
Dimethyl sulfoxide, oxidation of halides and esters, 882

2,2-Dimethyltetrahydropyran, 542
Dimethyltetralin, 410
2,4-Dimethyltricyclo[1.1.1.$0^{2,4}$]pentan-5-one, 118
Dimethyltriphenylphosphorus, 703
Dinaphthylhydrazines, 828
Dineopentyl ketone, 653
2,4-Dinitroanilinium ion, 225
m-Dinitrobenzene, nitration of, 397
Dinitrobenzenes, formation of, 383
Dinitrobromotoluene, 390
Dinitro compounds, formation of, 341, 547, 622, 887 (*see also* 970)
Dinitrodicarboxybiphenyls, 77, 78
2,4-Dinitrofluorobenzene, 502
Dinitrogen pentoxide, 388, 396, 397
Dinitrogen tetroxide, 614, 622
Dinitrogen trioxide, 485, 623, 880
2,4-Dinitrophenylhydrazones, 674
N,C-Dinitroso compounds, 399
Diols, conversion to cyclic ethers, 318
  formation of, 896, 897 (*see also* 971)
  oxidation to lactones, 883
1,2-Diols, cleavage of, 867–870
  conversion, to acetals, 661
    to aldehydes or ketones, 754
    to thionocarbonates, 768
  formation of, 307, 616, 893, 903
  rearrangement of, 798
1,3-Diols, conversion to acetals, 661
  formation of, 701, 711
  fragmentation of, 775
  reduction of, 349
gem-Diols, formation of, 655
1,4-Dioxane, 149, 150
1,3-Dioxanes, 711
2,4-Dioxo-1,3-diazetidines, 719
1,2-Diphenoxyethane, 549
Diphenylacetaldehyde, 787
Diphenylacetylene, 764
1,1-Diphenyl-2-amino-1-propanol, 784
1,4-Diphenyl-2,3-benzofuran, 632
1,4-Diphenylbutadiene, 629
1,4-Diphenylbutadiyne, 588
2,3-Diphenylbutane, 354
1,4-Diphenyl-2-butene, 768
Diphenylcarbene, 158*n*., 161
1,3-Diphenyl-2-chloropropanone, 806
1,4-Diphenylcyclohexenes, 629
1,5-Diphenylcyclooctene, 790
5,5-Diphenylcyclooctyl tosylate, 790
Diphenylcyclopropanone, 806
Diphenylcyclopropenium perchlorate, 49
Diphenylcyclopropenone, 49
1,1-Diphenylethanediol, 787
Diphenyl ether, 403
1,1-Diphenylethylene, 608
N,N′-Diphenyl-N,N′-ethylenediaminocarbene, 159
Diphenylketene, formation of, 810
  reaction with aldehydes and ketones, 723
  reduction of, 679
Diphenylmethane, alkylation of, 357
  condensation with benzophenone, 697
  formation of, 406
Diphenylmethyl carbanion, 144
Diphenylmethyl cations, 128
2,4-Diphenyl-8-oxabicyclo[3.2.1]octan-3-one, 806
Diphenylpicrylhydrazyl, 154
1,3-Diphenylpropane, 602
2,3,3-Diphenylpropiophenone, 604
1,2-Diphenylpropyltrimethylammonium ion, 733
2,3-Diphenylsuccinic acid, 879
2,5-Diphenylthiophene, 588
Diphenyltin dihydride, 681
1,3-Dipolar addition, 623–625
  in epoxidation, 620
  of ozone, 874
Dipole moments, 18
  of alkylbenzenes, 57
  determination of, 182, 198
  to determine configuration, 97
  to determine conformation, 109
Dipropylbenzenes, 433
Dipropylcyclopropenium perchlorate, 49
Dipropylcyclopropenone, 49
Dipropylferrocene, 434
Dipropyl fumarate, 70
Dipropyl maleate, 70
Diradical character, of aromatic compounds, 48, 51, 52
  of aryl cations, 492
Diradicals, 156
Disiamylborane, 599, 600
  selectivity, 892
Diskatole, 191
Disproportionation of radicals, 157
Disrotatory motion, 839–841
Dissociation energies, 24, 155
Disulfide ions, reaction, with alkyl halides, 329
    with aryl halides, 501
    with diazonium salts, 512
Disulfides, cleavage of, 764
  desulfurization of, 556
  formation of, 329, 330, 501, 888, 900 (*see also* 971)
  oxidation to sulfonic acids, 885
  reduction of, 902, 903
Disulfones, 280
Dithiatricyclooctacosatetraenedione, 557
Dithiatricyclotriacontatetraenedione, 557
Dithioacetals, 557
Dithio acids, 691
1,2-Dithioaroxyethylenes, 279, 280
Dithiocarbamates, 673
Dithiocarbethoxyaspartic acids, 85

Dithiocarbonates, 757
Dithiols, formation of, 665
Dithiophosphonates, 588
Divinylcyclobutanes, 835, 837
2,3-Divinyl-1,3-cyclohexadiene, 835
Divinylcyclopropanes, 835–837, 843
Divinylmethyl cations, 127–128
Diynes, coupling of, 549
  in Diels-Alder reaction, 628
  formation of, 549
DL system, 83–88
1-Dodecanol, 753
Doebner-Miller reaction, 423
Doebner modification, 698
d orbitals, 6
Double-bond character, 196
  in benzene, 28, 31
  in naphthalene, 39
Double-bond compounds, addition reactions of, 562–726
  electronic structure of, 13, 171–173
  formation of, 727–780, 861–867
  geometrical isomerism of, 94
Double bonds at bridgeheads, 122, 739, 751
Doublets, definition of, 153
Duff reaction, 420
Durene, 426, 436

E (bond energy), 25, 26, 29
Eclipsed conformations, 102, 103, 109, 119
Eclipsing effects, 109, 119–120
  in Ei eliminations, 748, 752
  in E2 eliminations, 733, 741, 742
  in rearrangement reactions, 787
Eigenfunctions, 3
Eigenvalues, 3
Ei mechanism, 747–752
  in Chugeav reaction, 757
  in cleavage of quaternary ammonium salts, 761
  in Cope reaction, 762
  in ester pyrolysis, 756
  in ether cleavage, 755
  in Hofmann elimination, 759
  in pyrolysis, of allyl ethers, 779
    of β-hydroxy olefins, 779
  in sulfoxide cleavage, 964
Elbs reaction (cyclodehydration), 410
Elbs reaction (hydroxylation), 539
Electrolysis of carboxylate ions, 557
Electron, size of unshared pair, 12
  wave nature of, 3
Electron-deficient nonclassical carbonium ions, 130, 136–140
Electron diffraction, 23, 97, 109, 198
Electron-donating groups, 20–21
  in addition to multiple bonds, 573, 575
  in electrophilic substitution, 384–387
Electron-donating groups, in nucleophilic substitution, 495, 497
Electron donation, by inductive effect, 20
  by resonance effect, 36
Electronegativity, 17–19
  determination of, 184, 193, 195
Electronic levels, 7, 168–171
Electronic spectra, 168–175
  of sodium fluorenide, 147
Electronic structures, 8–17
Electron paramagnetic resonance, 196, 205
  for detection of radicals, 153, 155
Electron spin, 7, 153, 156
Electron spin resonance (*see* Electron paramagnetic resonance)
Electron-sufficient nonclassical carbonium ions, 130–136
Electron transfer mechanisms, 855
Electron withdrawal, by inductive effect, 20
  by resonance effect, 36
Electron-withdrawing groups, 20–21
  in addition to multiple bonds, 573, 575
  effect on free radical abstraction, 528
  in electrophilic substitution, 384–387
  in nucleophilic substitution, 495, 497, 498
Electrophile, definition of, 200
Electrophiles, reactivity of, 393
Electrophilic addition to multiple bonds, 200, 562–567, 572
  orientation and reactivity in, 573–579
Electrophilic free radicals, 528, 531, 575
Electrophilic substitution, 200
  aliphatic, 442–487
  aromatic, 376–441
    in definition of aromaticity, 37
    of nonbenzenoid aromatic compounds, 42–45, 51–55
    orientation and reactivity in, 382–395
  at nitrogen atom, 484–487
α-Elimination, 163, 644, 727, 765
α'-β-Elimination, 761
β-Elimination, definition of, 727
γ-Elimination, definition of, 141, 727
1,4-Elimination, 753, 760, 771
1,6-Elimination, 866
Elimination-addition mechanism, in aliphatic hydrogen exchange, 453
  with carbamates, 313
  in nucleophilic substitution, 278, 492
  in rearrangements, 791*n.*, 798, 815
Elimination reactions, 201, 727–780, 859–867
  in bicyclic systems, 122
  bisdecarboxylation, 879
  elimination, of ammonia, 671
    of HBr from ylides, 704
    of hydrogen, 859–867
    of phosphine oxides, 705, 769
  to form carbonyl bond, 477–481, 560, 778–779

Elimination reactions, versus nucleophilic substitution, 728, 734, 738, 744–746
  orientation and reactivity, 738–747, 751
Elsevier's "Encyclopedia of Organic Chemistry," 944
Emde reaction, 351
Enamines, acylation of, 465, 482
  alkylation of, 464
  arylation of, 465
  conversion to lactams, 724
  2 + 2 cycloadditions of, 637, 724
  formation of, 590, 668, 671, 861 (*see also* 971)
  hydrolysis of, 658
  reaction with alkynes, 603
  tautomerism of, 62
Enantiomers, absolute configuration of, 82
  conversion to diastereomers, 92
  Cotton effects, 111
  creation of, 81
  properties of, 71–73
  representation of, 81
  separation of, 92
Enantiomorphs, 71
Endo addition in Diels-Alder reaction, 629, 635
Endo isomers, 100
Energy barriers to free rotation, 102
Energy levels of electrons, 7, 168–171
Energy of light, 168
Ene synthesis, 603, 841
Enol acetates, 359
Enolate ions, 60
  in aldol condensation, 692
  alkylation of, 357–361
  formation of, 357–360, 457, 458, 470
  in Michael-type reactions, 568
  resonance in, 35
  stability of, 144
Enol content of carbonyl compounds, 60
Enol esters, in anhydride formation, 325
  conversion to β-diketones, 365
  formation of, 319, 585, 587 (*see also* 971)
  hydrolysis of, 458
  transesterification of, 323
Enol ethers, addition of hypochlorites, 613
  conversion to aldehydes and ketones, 306, 307, 582
  2 + 2 cycloadditions of, 638
  formation of, 317, 585, 662, 704, 756, 771, 812 (*see also* 971)
  hydrolysis of, 458
  pyrolysis of, 756
  reaction with cyanic acid, 591
  rearrangement of, 848
Enol form in tautomerism, 59, 60
Enolization, of 5-methyl-3-phenyl-2-hexanone, 237
  as side reaction in Grignard addition, 685, 687, 689
Enol lactones, 625
Enols, 457
  in halogenation of carbonyl compounds, 459, 460
  in Michael-type reactions, 568
  reaction with ketene, 585
Enol thioethers, 588, 636
Enthalpy of activation, 213
Entropy of activation, 749
Envelope conformations, 109
Enynes, addition reactions, 575
  bromination of, 612
  in Diels-Alder reaction, 628
  formation of, 603
  reaction with carbenes, 646
E1 mechanism, 734–737
  orientation and reactivity, 739, 743–747
  versus S_N1, 734, 744–747
E1cB mechanism, 732, 735–737
  orientation and reactivity, 740, 743–746
E1-E2-E1cB spectrum, 737, 740, 743–746
Eosin, 622
Ephedrine, 92
epi as prefix, 88
Epinephrine, 922
Episulfides, amination of, 334
  conversion to alkenes, 769
  formation of, 722
  in nucleophilic substitution, 290, 302
Episulfones, 770
Epoxidation of alkenes and alkynes, 578, 617–621
Epoxides, amination of, 334
  conversion, to alkenes, 769
    to diols, 307
    to halohydrins, 345
    to hydroxy mercaptans, 328
    to hydroxy sulfides, 329
    to hydroxy sulfonic acids, 330
  formation of, 316, 618–621, 700, 720, 811 (*see also* 972)
  in nucleophilic substitutions, 290, 302
  oxidation of, 882
  reaction, with active hydrogen compounds, 361
    with alcohols, 319
    with cyanide ion, 361
    with Grignard reagents, 355
    with phosphines, 334, 708
    with phosphoranes, 356
  rearrangement of, 799
  reduction of, 350
  stereochemistry of ring opening, 579
  strain in, 290
1,4-Epoxycyclooctane, 543
Epoxy ketones, rearrangement of, 804
2,3-Epoxy-1-propanol, 289
Equatorial bonds in six-membered rings, 105–107
Equilibration of carbonyl compounds, 458

Equilibrium constants, correlated by Hammett equation, 239
  determination of, 174, 181, 192
Erlenmeyer azlactone synthesis, 699
erythro as prefix, 89
Eschweiler-Clarke procedure, 669, 670
Esterification, 319–324
  of benzoic acids, 233
  of enolates, 472
Ester intermediates in oxidation reactions, 856
Esters (*see* Carboxylic esters; Inorganic esters; etc.)
E_s values, 244, 245
Étard reaction, 880
Ethane, acidity of, 145
  bond energies of, 25
  conformations of, 102
  formation of, 153, 164, 468
Ethanol, in clathrate compounds, 70
  dehydration of, 755
  nmr spectrum, 183, 184, 186, 188
  reaction, with alkyl halides, 233
    with diazonium salts, 514
Ethanolamines, 334
Ethers, acyloxylation of, 545
  in alkylation of aromatic rings, 407
  autoxidation of, 544
  cleavage of, 306, 344, 755
  conversion to arylamines, 502
  coupling of, 549
  formation of, 312, 316–318, 323, 345, 350, 355, 472, 500, 542, 545, 557, 584, 612, 663, 824, 896, 902 (*see also* 972)
  hydration of, 583
  reaction, with organometallic compounds, 355, 506
    with sulfonic acids, 327
  rearrangement of, 429, 827, 830–834
  reduction of, 350, 438, 505
Ethoxide ions, reaction, with active hydrogen compounds, 357
    with esters, 366–368, 897
  reduction, of aldehydes and ketones, 680, 682
    of anhydrides, 896
    of C═N compounds, 682
    of double bonds, 592
    of nitriles, 683
    of nitro compounds, 907
    of oximes, 899
p-Ethoxyaniline, 519
Ethoxy sulfones, formation of, 280
Ethyl acetoacetate, addition, to activated olefins, 604
    to ethyl propynoate, 606
  alkylation of, 299, 358, 359
  condensation with aldehydes or ketones, 697
  dimerization of, 888
  reaction with alkenes, 713
Ethyl acetoacetate, tautomerism in, 60
Ethyl 2-acetoxycyclohexanecarboxylate, 751
Ethyl 2-acetyl-3-phenylpropenoate, 697
Ethylamine, 331
Ethylation of toluene, 395
Ethylbenzenes, dipole moment, 57
  ethylation of, 383
  isomerization of, 434
  oxidation of, 880
  reaction with Friedel-Crafts catalysts, 433
Ethyl benzoate, 277
Ethyl butylmalonate ion, 288
Ethyl carbanion, 145
1-Ethyl-4-carbomethoxypyridinium ion, 297
1-Ethyl-4-carbomethoxypyridinyl radical, 154, 529
Ethyl carbonate, in mixed Claisen condensations, 366
  reaction, with Grignard reagents, 363, 688
    with ketones, 368
    with malonamides, 340
    with nitriles, 369
Ethyl cation, 126, 197
Ethyl chloroformate, 362, 370
Ethyl cyanoacetate, 358, 604
Ethyl 2-cyclohexanecarboxylate, 751
Ethylene, acidity of, 145
  arylation of, 552
  bond angles of, 14
  conversion to acetaldehyde, 884
  deuterogenation of, 594
  as dienophile, 626, 628
  dimerization of, 602
  electronic spectrum of, 171
  electronic structure of, 13, 16, 35
  excited states of, 565
  formation of, 117, 755, 756, 838
  reaction, with alkanes, 601, 602
    with bromine, 565
    with butadiene, 603
    with carboxylate ions, 602
    with sulfuric acid, 584
    with xenon tetrafluoride, 611
Ethylene glycol, 908
Ethylene oxide, reaction with aromatic rings, 407
  strain in, 117
Ethyl (ethoxymethyl)malonate, 755
Ethyl formate, 367
3-Ethyl-2-heptanol, 91
3-Ethyl-2-heptanone, 91
3-Ethyl-3-heptene-2-ol, 91
4-Ethyl-4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxide free radical, 154
Ethyllithium, 148
Ethylmagnesium bromide, reaction, with free radical, 154
    with imines, 465
  structure of, 150

Ethylmagnesium chloride reaction with benzyl chloride, 353
Ethyl malonate, addition to activated olefins, 604, 698
  alkylation of, 357, 360
  condensation with aldehydes and ketones, 698
  halogenation of, 460
  reaction, with diazonium ions, 460
    with urea, 340
Ethyl mercaptan, 194
Ethylmercury chloride, 151
2-Ethyl-3-methyl-1-butene, 739
Ethyl methylenemalonate, 698, 755
Ethylmethylphenylarsine, 75–76
Ethyl nitrate, 396
Ethyl orthoformate, 671
Ethyl oxalate, 366
2-Ethylpentanoic acid, 357
3-Ethyl-1-pentene, 767
5-Ethyl-2-picoline, 667
Ethyl picrate, 489
5-Ethyl-5-propylundecane, 75
Ethyl propynoate, 606
3-Ethylpyridine, 510
2-Ethyltetrahydrofuran, 318
Ethyltoluenes, 409
Ethyl trichloroacetate, 644
Ethyltrimethylammonium ion, 737
Ethynyl carbanion, stability of, 145
Ethynylcyclopropanes, 646
1-Ethynyl-1-hydroxy-2,2,6-trimethylcyclohexane, 272
E2 mechanism, 728–733, 737
  eclipsing effects, 733, 741–742
  orientation and reactivity, 739–747
  versus S_N2, 728, 738, 744–746
Excited molecules, fate of, 174
Excited states, of ethylene, 565
  of hydrogen atom, 7
  hyperconjugation in, 58
  reactions of, 175
Exo addition in Diels-Alder reaction, 629, 635
Exo attack in solvolysis of norbornyl systems, 136
Exocyclic double bonds, optical activity from, 79
Exo-endo isomerism, 100
Exo-endo rate ratios in solvolysis of norbornyl systems, 137, 138
Extinction coefficients, 170
  in circular dichroism, 114

Far infrared spectra, 175
Far ultraviolet spectra, 169
Favorskii reaction, 698
Favorskii rearrangement, 804–809
Fehling's solution, 539
Fenton's reagent, 539, 549
Ferric chloride, in aminations, 400
  in arylations, 412
  in cyanogenation, 425
  in Friedel-Crafts reactions, 407, 411
  in halide coupling, 354
  in halogenations, 403
  in ketone synthesis, 362
  in nitrations, 397
  reaction with aromatic rings, 405
Ferricyanide, 857*n*.
Ferrocenes, 42
  arylation of, 550
  cyanogenation of, 425
  disproportionation of, 434
  formation of, 434
  formylation of, 418
  optical activity of, 80
  (*See also* Metallocenes)
Ferrous ions reaction with hydroperoxides, 824
Ferrous sulfate, 538
Field effects, 19
Fingerprint region of infrared spectrum, 178, 179
Finkelstein reaction, 342
First-order reactions, 208, 212
Fischer-Hepp rearrangement, 430
Fischer indole synthesis, 844
Fischer projection, 81
Flexible conformation, 105
Fluoborate ions, reaction with diazonium salts, 513
  reduction of nitro compounds, 907
Fluoboric acid, 317
Fluorene, acidity of, 41, 220
  carbanion from, 146
  metalation of, 469
  naming of, 928
Fluorenes, 604
Fluorescence, 174
Fluoride ions, reaction, with acyl halides, 343
    with alkenes, 611
    with alkyl halides, 342
    with aryl chlorides, 504
Fluorinated alkenes conversion to fluorinated cyclobutanes, 636, 637
Fluorination, of alkanes, 533
  of alkenes, 611
  of aromatic rings, 405, 611
Fluorine atoms, 527
α-Fluoroamines, 344
Fluorobenzene, 418
4-Fluorobutanoic acid, 558
Fluorocyclohexane, 181
4-Fluoro-3,5-dimethoxyphenol, 405
1-Fluoro-3,3-dimethyl-1-butyne, 642

Fluoroethane, 379
Fluoroformates, 504
Fluorohydrins, 612
Fluoromethanes, 59
5-Fluoropentanoic acid, 558
Fluorosulfuric acid, 126, 128, 402
9-Fluoryllithium, 469
Fluxional structures, 842
^{19}F nmr, in conformational analysis, 192
  to measure resonance effects, 243
f orbitals, 6
Formal charge, 16
Formaldehyde, in aminoalkylation, 424
  condensation, with aldehydes and ketones, 701
    with ethyl malonate, 698
    with nitro compounds, 702
    with phenols, 422
  in crossed-Cannizzaro reaction, 908
  in haloalkylation, 424
  hydration of, 655
  in Mannich reaction, 670–672
  polymerization of, 717
  reaction, with alcohols and hydrogen halides, 676
    with alkenes, 711
    with alkynyl ethers, 714
    with amines, 657
    with ammonia, 666
    with cyanide ion and ammonia, 710
    with diazonium salts, 514
    with organometallic compounds, 684
  in reductive alkylation, 669
Formaldehyde dimer, 712
Formamides, conversion, to aldehydes, 363
    to isonitriles, 778
  formation of, 334, 669, 715, 725
  in formylation, of aromatic rings, 417
    of olefins, 463
  reaction, with alkenes, 606, 616
    with Grignard reagents, 689
  in reductive alkylation, 669
Formates, addition to olefins, 606
  conversion, to aldehydes, 363
    to *gem*-dihalides, 677
  formation of, 823
  reaction, with Grignard reagents, 688
    with ketones, 368
Formazans, 460
Formic acid, acidity of, 19
  conversion to aldehydes, 371
  decarbonylation of, 315
  formation of, 304, 868
  in formylation of amines, 336
  in hydrocarboxylation, 608
  in lactone formation, 587
  in Mannich reaction, 671
  in nitrile formation, 675
Formic acid, reaction, with alcohols, 663
    with alkenes and hydrogen peroxide, 617
    with chlorosulfuric acid, 417
  in reductive alkylation, 669
Formic anhydride, 336, 416
Formic anhydrides, mixed, 336, 414, 416
Formylation, of amines, 336
  of aromatic rings, 414, 416–420
  of olefins, 463
Formyl chloride, 416, 417
2-Formylcycloalkanones, 871
Formyl fluoride, 418
13-Formyl-13-norcorticosterone-21-acetate, 850
2-Formylpyrrole, 419
Four-center reactions, 202
Fractional crystallization, 92
Fractional distillation, 93
Fragmentation reactions, 543, 772–777
Franck-Condon principle, 174
Free-energy differences between axial and equatorial substituents, 107
Free-energy requirements for reaction, 202
Free-radical abstraction, 157, 523–529
  internal, 542, 793, 849, 851
Free-radical addition to multiple bonds, 202, 570, 573, 652
  reactivity and orientation, 575, 577, 578
Free-radical eliminations, 750
Free-radical polymerization, 570
Free-radical reaction mechanisms, 199, 201, 521
Free-radical rearrangements, 202, 790
Free radicals, 125, 153–158
  bridged, 525, 571
  from carbanions, 152, 544
  from carbenes, 166
  destruction of, 157, 521
  detection of, 205
  epr and, 196
  formation of, 157, 521, 855
  generation and fate, 157
  hyperconjugation in, 58
  oxidation of, 855
  reactivity of, 531
  reduction of, 855
  stability, 155
  structure, 155
Free-radical substitution, 201, 521–561
Free valence, 55, 391
3β-Friedelanol, 796
Friedel-Crafts acylation, 413–416
  aliphatic, 463
  of alkylbenzenes, 381, 391
  of bromofluorobenzene, 389
  with nitriles, 424
Friedel-Crafts alkylation, 406–412
  of alkylbenzenes, 379, 395

Friedel-Crafts, alkylation, of olefins, 601
  reversal of, 433
Friedel-Crafts arylation, 412
Friedelene, 797
Friedelin, 113, 796
Friedlander quinoline synthesis, 667
Fries rearrangement, 428
Fritsch-Buttenberg-Wiechell rearrangement, 811
F-strain, 229
Fully-eclipsed conformation, 104
Fulvenes, 41
  formation of, 697, 698
  reaction with Grignard reagents, 650
Fumaric acid, bromination of, 565
  properties of, 96, 97
  reaction with bromine, 101
Fumaric acid-iron-tetracarbonyl, 80
Furan, aromaticity of, 40
  in Diels-Alder reaction, 628, 632
  orientation in, 390
  reaction with diphenylcyclopropanone, 806
  reduction of, 597
Furans, acylation of, 414
  alkylation of, 408
  conversion to 1,4-diones, 307
  formation of, 662
Furfural, 318
Furfuryl alcohol, 755
Fused ring systems, acylation of, 413
  carboxylation of, 420
  geometrical isomerism of, 99
  naming of, 926–928, 930
  orientation in, 390
  structure of, 39
Fusion names, 926

Gabriel synthesis, 340
Gallium bromide, 395, 409
Gallium chloride, 407
Gatterman amide synthesis, 420
Gatterman-Koch reaction, 417
Gatterman method (biaryl formation), 555
Gatterman reaction (formylation), 417
Gatterman reaction (halide formation), 554
Gauche conformation, 103, 119
Gegen-ions, 125
General acid and base catalysis, 226, 227
  of hydrate formation, 656
Geometrical isomerism, 94–100
Geometric isomers, methods of distinguishing, 97
  properties of, 96
Girard's reagents, 674
Glaser reaction, 549
Glucose, 907
Glyceraldehyde, 83, 84
Glyceric acid, 83
Glycerol, 423
Glycidic acids, decarboxylation of, 478
Glycidic esters, formation of, 619, 700
Glycine, 902
Glycols (*see* Diols)
Glyoxal, benzoin condensation of, 714
  cleavage of, 868
  formation of, 872
Gomberg-Bachmann pinacol synthesis, 903
Gomberg-Bachmann reaction (arylation), 550
Grignard reaction, 684
Grignard reagents, abstraction of protons, 469
  1,4 versus 1,2 addition, 604
  addition to olefins, 604, 650
  conjugate addition of, 604
  conversion, to alkenes, 685, 768
    to *tert*-butyl ethers, 472
  coupling of, 555
  formation of, 475, 650, 815
  hydrolysis of, 440, 470
  optically active, 445
  reaction, with acid derivatives, 362–363, 688
    with aldehydes, 92, 684
    with alkyl halides, 353
    with alkynes, 440
    with aromatic ethers, 506
    with benzils, 803
    with carbon dioxide, 689
    with carbon disulfide, 691
    with C=N compounds, 465, 689, 691
    with epoxides, 355
    with ethers, acetals, and ortho esters, 355
    with halogens, 473
    with isocyanates, 691
    with ketones, 684
    with metal halides, 474
    with nitriles, 691
    with oxygen, 471
    with sulfates and sulfonates, 355
    with sulfonyl halides, 375
    with sulfur, 473
  rearrangement of, 815
  structure of, 149–151
Grignard's "Traité de chimie organique," 950
Ground state of atoms, 7–12
Group electronegativities, 18
Grunwald-Winstein equation, 296, 298
S-Guaiazulene, 45
Guaiol, 45
Guerbet reaction, 888
Guest in inclusion compounds, 69, 70

H_0 and similar functions, 224–225
Half-chair conformation, 109
Half-life of first-order reactions, 212
Halide exchange, 342, 503

Halide ions, in decarboxylative halogenation, 559
  exchange, with alkyl halides, 295, 342
    with aryl halides, 503
  as leaving groups, in aliphatic substitution, 290
    in aromatic substitution, 490, 493, 494, 498
    in eliminations, 745–746, 750
  as nucleophiles, 288
  reaction with sulfates and sulfonates, 343
Haller-Bauer reaction, 483
Halo acetals, conversion to enol ethers, 771
  formation of, 459, 613
Halo acids, conversion, to amino acids, 331
    to lactones, 323
  decarboxylation of, 477
  formation of, 460
β-Halo acrylic acids, fragmentation of, 774
N-Halo-N-acylamines, 431
p-Halo-N-acylamines, 431
α-Halo acyl halides, conversion to ketenes, 771
  formation of, 612
α-Halo alcohols, formation of, 676
γ-Halo alcohols, fragmentation of, 773
Halo aldehydes, 458
Haloalkylation, 406, 424
α-Halo amides, condensation with aldehydes and ketones, 701
  rearrangement of, 817
  in Reformatsky reaction, 687
N-Halo amides, 817
  formation of, 487
  reaction, with alkenes, 535
    with isonitriles, 726
  rearrangement of, 850
Haloamines, conversion to olefins, 772
  formation of, 614, 849
  fragmentation of, 773
N-Haloamines, addition to multiple bonds, 614
  formation of, 487
  rearrangement of, 849
Halocarbenes, addition to multiple bonds, 643*n*., 644
  insertion reactions of, 466
  reaction, with aromatic rings, 647
    with phosphines, 703, 704
Halo esters, condensation with aldehydes and ketones, 700
  conversion to olefins, 772
  formation of, 612, 618, 716
  reaction with alkenes, 649
  in Reformatsky reaction, 687
Halo ethers, conversion to alkenes, 771
  formation of, 612, 613, 676
Haloformic esters, formation of, 319
Haloform reaction, 482
Halogenation, of acetals, 459
  of acids and acyl halides, 460
  of aldehydes and ketones, 458
  of anhydrides, 460
  of aromatic rings, 403
  of esters, 458
  free-radical, 532–538
  of multiple bonds, 610
  of nitro compounds, 460
N-Halogenation, 487
1-Halohexafluorocyclobutanols, 676
Halohydrins, formation of, 345, 612
N-Halo imides, formation of, 487
α-Halo iminium salts, 684
Halo ketones, condensation with aldehydes and ketones, 701
  formation of, 345, 458, 463, 612, 616 (*see also* 973)
  reaction with alkenes, 649
  rearrangement of, 804
β-Halo nitrates, formation of, 614
Halo nitriles, condensation with aldehydes and ketones, 701
  reaction with alkenes, 649
  in Reformatsky reaction, 687
Halo nitro compounds, formation of, 614
Halo nitroso compounds, formation of, 613
Halo oximes, formation of, 614
β-Halo sulfides conversion to olefins, 772
N-Halo sulfonamides, formation of, 487
Halosulfonation of aromatic rings, 402
Halo sulfones, conversion to alkenes, 770
  formation of, 613
Halo thioethers, formation of, 613
Halo tosylates conversion to olefins, 772
Halo α,β-unsaturated esters in Reformatsky reaction, 687
Hammett acidity function, 224
Hammett equation, 238–241, 498
  in electrophilic substitution, 393
  in nucleophilic substitution, 285
Handbooks, 944
"Handbuch der organischen Chemie" (Beilstein), 942–944, 952
Hantzsch-Widman system, 921, 930
Hauser rearrangement, 517
Haworth reaction, 415
Heat, of atomization, 25
  of combustion, 25, 120
Helical-shaped molecules, optical activity of, 80
Hell-Volhard-Zelinskii reaction, 460
Hemiacetals, 582, 662, 663
Hemiaminals, formation of, 666–672
Hemihydrates, 655, 656
Hemimercaptals, 665
Hemithioacetals, desulfurization of, 557
Henkel reaction, 436

1,5-Heptadiene, 834
2,5-Heptadiene, 95
Heptafulvene-8,8-dinitrile, 44
Heptafulvenes, 44
Heptaldehyde, 779
Heptalene, 44
Heptanes, 601
2-Heptanone, 359
Heptaphenylcycloheptatrienyl anion, 52
Herz reaction, 403
Hetarynes, 494*n*.
Heterocyclic compounds, acylation of, 414
  alkylation of, 408
  formation of (*see* 973)
  formylation of, 418, 419
  naming of, 928–930
  orientation in, 390
  reaction with nitriles, 425
Heterolytic reactions, 199
Hexabromocyclohexane, 611
Hexachlorocyclohexane, 729–731
  formation of, 611
  isomers of, 99
Hexacyclo[6.2.1.$1^{3,6}$.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]dodecane, 118
1,4-Hexadiene, 603, 841
1,5-Hexadiene, 758, 801
2,4-Hexadienes, 838–841
Hexadienols, 273
1,5-Hexadiyne, 549
Hexafluorobenzene, 506
1,1,1,4,4,4-Hexafluoro-2,3-diphenyl-2,3-butanediol, 787
2,2a,3,3a,4,5-Hexahydro-1*H*-cyclopent[*jkl*]-*as*-indacene, 37
1,2,3,6,7,8-Hexahydro-*as*-indacene, 37
Hexahydronaphthalene, 629
Hexaisopropylbenzene, 123, 642
Hexamethylacetone, conversion to oxime, 675
  formation of, 689
  reactivity, 653
Hexamethylenetetramine, formation of, 666
  in formylation of aromatic rings, 420
  in oxidation of benzylic halides, 883
  reaction with alkyl halides, 332
1,6-Hexanediol, 318
Hexanes, 601
Hexanoic acid, 871
1,1,1,4,4,4-Hexaphenylbutane, 792
Hexaphenylethane, 154, 156
Hexaphenylpentalene, 45
Hexatrienes, rearrangement of, 835, 839–841
Hexene, isomerization of, 456
Hexenes, ozonolysis of, 873, 874
5-Hexen-1-ol, 801
5-Hexenyldimethylamine, 758
5-Hexenyltrimethylammonium hydroxide, 758
Hex-3-en-5-yn-2-one, 590
Hex-5-en-3-yn-2-one, 590
Hexihelicene, 80
3-Hexyne, 584
Highest-occupied orbitals, 633–636, 839–841
High-resolution mass spectrometry, 197
Hill system, 941, 943
Hinsburg test, 374
Hoesch reaction, 424
Hofmann degradation, 758
Hofmann exhaustive methylation, 758
Hofmann-Löffler reaction, 849
Hofmann-Martius reaction, 432
Hofmann rearrangement, 783, 816
Hofmann's rule, 740–742, 746, 751
  in dehydration, 754
  in pyrolysis of quaternary ammonium hydroxides, 759, 760
  in sulfone cleavage, 764
  in sulfoxide cleavage, 764
Homoallylic carbonium ions, 130
Homoallylic rearrangements, 450
Homoaromatic carbonium ions, 131
Homogeneous reactions, kinetics, 208
Homologization of aldehydes and ketones, 810
Homolytic reactions, 199, 521
3,4-Homotropylidene, 842
Hooker oxidation, 852
Horner reaction, 705
Host in inclusion compounds, 69, 70
"Hot" carbonium ions, 291
Houben-Hoesch reaction, 424
Houben-Weyl's "Methoden der organischen Chemie," 949
Huang-Minlon modification, 893
Hückel's rule, 48–54
Hund's rule, 7, 48, 160
Hunsdiecker reaction, 529, 559
  neighboring group assistance in, 526
Hybridization, determination of, 195
  digonal, 11
  effect on acid and base strength, 229
  of orbitals, 10–13
  tetrahedral, 12
  trigonal, 11
  in water and ammonia, 12
Hydantoin, 700
Hydrates, formation of, 655
Hydration, of aldehydes and ketones, 655
  of double-bond compounds, 566, 581, 584
  of triple-bond compounds, 582
Hydrazide ion reaction with alkenes, 876
Hydrazides, conversion to acyl halides, 347
  formation of, 335, 338
  hydrolysis of, 313
  reaction with nitrous acid, 818
Hydrazine, conversion to hydrazides, 335, 338
  reaction, with hydrazones, 675
    with phenacyl bromides, 867
  reduction, of aldehydes and ketones, 893–894
    of aryl halides, 440

Hydrazine, reduction, of double bonds, 592, 596
    of nitro compounds, 897, 908
    of sulfonyl chlorides, 374
    of tosylates, 505
Hydrazines, addition to multiple bonds, 590
  conversion, to azides, 485
    to azo compounds, 867
    to indoles, 844
  formation of, 510, 590, 657, 817, 899–900 (*see also* 975)
  reaction, with aldehydes and ketones, 674
    with nitrogen heterocycles, 510
  (*See also* Hydrazo compounds)
Hydrazobenzenes, rearrangement of, 828
Hydrazo compounds, conversion to azo compounds, 867
  formation of, 899–900, 908
  reduction of, 902
  (*See also* Hydrazines)
Hydrazoic acid, in Passerini reaction, 726
  reaction, with alcohols, 820
    with aldehydes, 676, 820
    with aromatic rings, 400
    with carboxylic acids, 819, 820
    with ketones, 819–821
    with olefins, 820
Hydrazones, conversion, to azo compounds, 867
    to indoles, 844
  formation of, 460, 461, 674, 675, 867, 876
  hydrolysis of, 657
  reaction, with diazonium ions, 460
    with hydrazine, 675
    with hydrogen cyanide, 711
  reduction of, 682
  in Wolff-Kishner reaction, 894
Hydride ion in reduction of aldehydes and ketones, 680
Hydride shifts, 138, 141, 786–789, 795, 848
Hydride transfer mechanisms, 855
Hydrobenzamides, 666
Hydroboration, 456, 599
Hydrocarbons, resolution of, 93
Hydrocarboxylation of alkenes, 608
Hydroformylation, 609
Hydrogen, as acid, 471
  as neighboring group, 268
  reaction, with alkenes and carbon monoxide, 609
    with platinum, 596
  in reductive alkylation, 663, 668
  (*See also* Hydrogenation; Hydrogenolysis)
Hydrogenation, of aldehydes, 663, 668, 680, 893
  of alkenes, 576, 591–596
  of alkynes, 593–594
  of amides, 895
  of anhydrides, 896
  of aromatic rings, 597–599
Hydrogenation, of azo compounds, 899–900
  of C=N compounds, 682
  of esters, 896
  indirect, 581
  of ketones, 663, 680, 893
  mechanism, 594
  of nitriles, 683
  of nitro compounds, 897
  of oximes, 899
  of ozonides, 871
  of phenols, 505
  selectivity, 890, 892
  of small rings, 117
Hydrogen atoms, in catalytic hydrogenation, 595
  potential energy of, 4
  wave equation for, 4
Hydrogen bonding, 63–65
  detection of, 180, 194
  effect on acid and base strength, 228
Hydrogen bromide, acidity of, 224
  addition, to double bonds, 455, 565–577, 579–582
    to triple bonds, 570, 571
  in haloalkylation, 424
  in isomerization of xylenes, 433
  reaction, with alcohols, 343
    with amines, 346
    with 3-bromo-2-butanol, 264
    with cyclopropanes, 579
    with diazo ketones, 346
    with diazonium salts, 554
    with ethers, 344
Hydrogen chloride, addition to alkenes, 566, 576, 577, 580
  in formylations, 417
  in haloalkylation, 424
  in Hoesch reaction, 424
  in Pinner synthesis, 664
  reaction, with aldehydes and ketones, 676
    with alkylbenzenes, 380, 382
    with butadiene, 573
    with diazo ketones, 346
    with diazonium salts, 554
    with hydrazides, 347
    with nitro compounds, 504
Hydrogen cyanide, addition to multiple bonds, 610, 710, 711
  hydrogen bonding of, 65
  reaction, with aldehydes, 90–91, 710
    with aromatic rings, 417, 425
    with carbonium ions, 715
    with C=N compounds, 711
    with ketones, 90, 710
Hydrogen exchange, in aliphatic systems, 143–145, 448, 452, 458, 594
  in aromatic systems, 396
Hydrogen fluoride, in Friedel-Crafts alkylation, 407

Hydrogen fluoride, in lactone formation, 587
  reaction, with acyl halides, 343
    with alkenes, 574, 580, 611
      and nitric acid, 614
    with alkylbenzenes, 380, 382
    with alkyl halides, 342
  in rearrangement of ethylbenzene, 433
Hydrogen halides, addition, to enynes, 575
    to multiple bonds, 580
  reaction, with aldehydes and ketones, 676
    with epoxides, 345
Hydrogen iodide, addition to multiple bonds, 577, 580
  in haloalkylations, 424
  reaction, with alcohols, 343
    with alkyl halides, 348
    with amines, 346
    with diazo ketones, 346
    with epoxides, 345
    with ethers, 344
  reduction, of aryl halides, 440
    of diketones, 894
    of sulfonyl halides, 900
Hydrogen molecule, canonical forms, 9
Hydrogenolysis, of acyl halides, 351
  of alcohols, 349
  of alkyl halides, 348
  of amines, 351
  of aryl halides, 440
  of cyclopropane, 579
  definition of, 348
  of epoxides, 350
  of hemiaminals, 669
  of hydroperoxides, 901
  of α-hydroxy ketones, 893
  of sulfur compounds, 556
Hydrogen peroxide, 857*n*.
  cleavage, of diketones, 868
    of 2-formylcycloalkanones, 871
  oxidation, of aldehydes, 878
    of alkanes, 538
    of amines, 884, 886
    of arenes, 538
    of boranes, 889
    of sulfur compounds, 887, 888
    of thiol esters, 885
  in peroxide formation, 326
  reaction, with alcohols, 824
    with alkenes, 617, 619, 620
      and azide ions, 623
    with Bunte salts, 329
    with ketones, 824
    with naphthoquinones, 852
    with nitriles, 660
    with ozonides, 871
Hydrogen sulfide, addition to multiple bonds, 587, 664, 665
  bond angles of, 24
Hydrogen sulfide, reaction, with acid derivatives, 329
    with alkyl halides, 328
  reduction of diketones, 894
Hydrolysis, of acetals, 306
  of acyl halides, 308
  of alkyl halides, 303
  of amides, 313
  of anhydrides, 309
  of aryl compounds, 499
  of Bunte salts, 328, 330
  of C=N compounds, 656
  of diazo ketones, 306
  of diazonium ions, 305, 512
  of dihalides, 303
  of epoxides, 307
  of esters, 310
  of inorganic esters, 305
  of isocyanates, 658
  of isothiocyanates, 658
  of nitrates, 778
  of nitriles, 660
  of nitro compounds, 658
  of organometallic compounds, 440, 470
  of ortho esters, 306
  of sulfonic acid derivatives, 305, 373
  of thiocyanates, 661
  of trihalides, 304
  of vinyl ethers, 306
Hydroperoxides, conversion to peroxides, 545
  formation of, 325, 471, 543, 589 (*see also* 975)
  reaction with acyl halides, 326
  rearrangement of, 824
  reduction of, 901
Hydroperoxy sulfides, 589
Hydroquinone, 70, 915
Hydroquinones, formation of, 679, 861, 878
Hydroxamic acids, formation of, 335, 338, 659
  rearrangement of, 819
Hydroxide ions, in Favorskii rearrangement, 804
  reaction, with active hydrogen compounds, 357
    with aldehydes, 908
    with alkyl halides, 303, 746, 765
    with chlorobutenes, 270
    with chloroquinones, 278
    with chlorosuccinic acid, 253
    with cyclooctene oxide, 848
    with DDT, 304
    with 2,2-dibromocyclodecanone, 121
  reduction of, 908
Hydroxy acids, cleavage of, 868
  conversion to nitrosophenols, 436
  cyclization of, 320
  decarbonylation of, 315
  decarboxylation of, 699

Hydroxy acids, formation of, 310, 420, 511, 660, 699, 710, 803, 804, 909 (*see also* 975)
  fragmentation of, 775
Hydroxy aldehydes, cleavage of, 693, 868
  formation of, 692, 693, 802, 850, 882 (*see also* 975)
  reaction with hydrazines, 674
  rearrangement of, 802
Hydroxyalkylation, 421
Hydroxy amides, formation of, 668, 687, 847 (*see also* 975)
  rearrangement of, 817, 847
Hydroxyamines, cleavage of, 868
  formation of, 334, 424, 519, 539, 666, 667, 690 (*see also* 975)
  fragmentation of, 774, 775
  rearrangement of, 799
  ring expansion of, 800
Hydroxy azo compounds, formation of, 851
p-Hydroxybenzaldehyde, 878
Hydroxybenzoic acids, 228
2-Hydroxybicyclo[2.2.1]heptan-7-one tosylate, 138
3β-Hydroxycholestan-5α,6α-episulfide, 115
4-Hydroxycinnoline, formation of, 461
1-Hydroxycyclopentylcarbinylamine, 800
2-Hydroxy-2-cyclopropylpropane, 273
2-Hydroxycyclotetratriacontanone, 905, 906
3-Hydroxy-1,5-dienes, 834
10-Hydroxy-9,10-dihydrospiro[anthracene-9,1′-cyclopropane], 135
4-Hydroxy-2,6-dimethyl-1,3-dioxane, 694
N-(1-Hydroxy-1,2-diphenylethyl)pyridinium ion, 697
Hydroxy esters, formation of, 322, 687, 696, 713, 803, 845 (*see also* 976)
Hydroxy ethers, formation of, 319
2-Hydroxyethyl *o*-nitrophenyl sulfoxide, 520
19-Hydroxy-18-hexatriacontanone, 904
Hydroxy ketones, in aldol condensation, 694
  cleavage of, 693, 868
  Clemmensen reduction of, 893
  formation of, 306, 428, 692, 693, 714, 802, 803, 904 (*see also* 975)
  reaction with hydrazines, 674
  rearrangement of, 802
Hydroxy ketoximes conversion to nitriles, 776
Hydroxylamine, addition to multiple bonds, 590
  amination of aromatic compounds, 510
  conversion to hydroxamic acids, 335, 338
  reaction, with acetamide, 275
    with aldehydes and ketones, 238, 675
    with thiones, 700
Hydroxylamine-N,N-bissulfonic acid, 675
Hydroxylamines, formation of, 590, 683, 761, 884, 898 (*see also* 976)
  oxidation of, 867, 884
Hydroxylamines, reaction, with aromatic rings, 400
    with nitroso compounds, 907
  rearrangement of, 519
  reduction of, 898
Hydroxylamine-O-sulfonic acid, reaction, with aldehydes and ketones, 675
    with aromatic rings, 400
    with boranes, 591
  reduction, of double bonds, 593, 596
    of sulfonamides, 351
Hydroxylation, at aliphatic carbon, 538
  of alkenes, 616
  of aromatic acids, 511
  of aromatic rings, 426, 538
Hydroxy mercaptans, formation of, 328, 664
2-Hydroxy-5-methylbenzaldehyde, 419
2-Hydroxy-1-morpholino-2-phenylpropiophenone, 813
7-Hydroxy-1,3-naphthalenedisulfonic acid, 379
Hydroxynaphthoquinones, 852
4-Hydroxy-1-naphthalenesulfonic acid, 379
Hydroxy nitriles, formation of, 361, 687, 710
α-Hydroxyphenylacetaldoxime, 899
2-(*p*-Hydroxyphenyl)ethyl bromide, 266
o-Hydroxyphenyl *o*-nitrophenyl sulfone, 519
1-Hydroxy-3-phenylpropane-1,3-disulfonic acid, 589
4-Hydroxypyridine, 61
Hydroxy sulfides, formation of, 329, 665
Hydroxy sulfonic acids, formation of, 330, 665
(2-Hydroxy-1,2,2-triphenylethyl)trimethylammonium ion, 518
Hydroxy α,β-unsaturated aldehydes and ketones, 694
1-Hydroxy-2-vinylcycloalkanes, 842
Hyperconjugation, 56–59
  in alkenes, 173, 739
  in aromatic systems, 386
  in carbonium ions, 126
  in free radicals, 153
  and σ values, 243
Hyperconjugative resonance effect, 58
Hypobromite ions, reaction, with amides and imides, 487, 816
    with amines, 487, 866
    with hydrazines, 867
    with sulfonamides, 487
Hypobromous acid, addition to multiple bonds, 577, 579, 612
Hypochlorite ions, oxidation of arene side chains, 877
  reaction with nitrogen compounds, 487
Hypochlorites, decomposition of, 560
Hypochlorous acid, addition to multiple bonds, 577, 612
  reaction with aromatic rings, 404, 405
Hypoiodous acid, 612

Hypophosphorous acid, 513
Hypsochromic shifts, 172

+*I* and −*I* groups, 21
Imidates (*see* Imino esters)
Imidazoles, 353
Imidazolides, 323, 326
  in ester formation, 322
  hydrolysis of, 314
Imides, N-acylation of, 340
  addition to multiple bonds, 590
  N-alkylation of, 340
  formation of, 237, 335, 336, 340, 716, 719 (*see also* 976)
  halogenation of, 487
  hydrolysis of, 313
  rearrangement of, 817
  reduction of, 895
  (*See also* Ureides, formation of)
Imidines, formation of, 673
Imine-enamine tautomerism, 62
Imines, bimolecular reduction of, 903
  condensation, with active hydrogen compounds, 698
    with ketones, 695
  conversion to aziridines, 722
  formation of, 462, 590, 666–669, 691, 709, 818, 866, 883 (*see also* 977)
  geometrical isomerism of, 95
  hydrolysis of, 656, 691
  in Passerini reaction, 726
  reaction, with Grignard reagents, 465, 689
    with hydrogen cyanide, 711
    with hydrogen sulfide, 665
    with ketenes, 724
    with phosphorous ylides, 708
  reduction of, 682
  in reduction of nitriles to aldehydes, 684
Iminium salts, formation of, 668
  hydrolysis of, 464, 658, 684
  reaction, with cyanide ion, 711
    with diazomethane, 723
    with Grignard reagents, 690
  reduction of, 682
1,6-Iminocyclodecapentaene, 54
Imino esters, conversion to ortho esters, 664
  formation of, 664, 849
  rearrangement of, 848
Imino ketones, 671
Imino nitriles, 709
2-Imino-4-thioxo-1,3-diazetidines, 719
Inclusion compounds, 69, 93
Indane, 924
Indanone, 414
3-Indazolones, 515
Indene, acidity of, 41, 221
  addition to activated olefins, 604
Indene, reaction, with carbenes, 648
    with DBr, 566
Index Chemicus, 941, 953
Indexing, of Beilstein, 943
  of *Chemical Abstracts,* 940–941
  of names, 923
Indicated hydrogen, 927, 929
Indoles, formation of, 844
  formylation of, 419
  ring expansion of, 647
Induced ring current (*see* Ring current)
Inductive effect, 19–21
  and acid and base strengths, 228
  in alkylbenzenes, 57
  in aromatic substitution, 384–388
  in carbanions, 143, 145
  in carbonium ions, 126
  in elimination orientation, 740
  and reactivity, 231, 242–243
  studied by nmr, 193
Infrared spectroscopy, 175–181
Inhibitors, free-radical, 522
Initial ozonides, 872, 874
Initiation steps, 521
Initiators, free-radical, 523
Inorganic esters, formation of, 326, 341, 504, 584, 889 (*see also* 977)
  hydrolysis of, 305
  pyrolysis of, 757
Insertion reactions of carbenes and nitrenes, 164, 466
Instrumental methods, 110–116, 167–198
Intermediate complex mechanism, 488
  reactivity in, 494–496, 498
Intermediates in mechanisms, 205
Internal return, 259
Intimate ion pairs (*see* Ion pairs)
Inversion of configuration, in electrophilic substitutions, 447, 450
  in nucleophilic substitutions, 252–255, 260, 262, 269
  at primary carbon, 254
  in rearrangements, 784–786
  at sulfur, silicon, and phosphorus, 254
Iodide ion, reaction, with Bunte salts, 329
    with diazonium ions, 512
    with dihalides, 729, 770
Iodination, of alkanes, 533
  of aromatic rings, 405, 406
  of multiple bonds, 611
Iodine, in alcohol dehydrogenation, 754
  in complex formation, 69
  in haloform reaction, 482
  in halogenations, 403
  in nitrile formation, 676
  reaction, with alkenes, 455, 571, 611
      and dinitrogen tetroxide, 614
      and peracetic acid, 618

Iodine, reaction, with alkenes, and silver carboxylates, 618
    with β-keto ester salts, 888
    with silver carboxylates, 559
    with thiol acids, 889
  in reduction of alcohols, 349
Iodine bromide, addition to alkenes, 611
  in complex formation, 69
Iodine chloride, addition to alkenes, 611
  in complex formation, 69
  reaction with aromatic rings, 405, 406
Iodine pentafluoride, 866
β-Iodo acetates, formation of, 618
Iodobenzene, 507, 508
β-Iodo benzoates, formation of, 618
Iodoethane, reaction, with enolate ions, 146
    with phenols, 301
Iodofluorination of alkenes, 611
Iodoform, 482, 483
Iodohydrins, conversion to alkenes, 769, 772
  formation of, 612
  rearrangement of, 799
Iodomethane, in clathrate compounds, 70
  formation of, 344, 648
  reaction, with amines, 758
    with chloride ion, 295
    with dithiocarbonates, 757
    with epoxides, 770
    with phenols, 300
Iodonium salts, 491*n*., 507
2-Iodopropane, 301
Ionic bonds, 18
Ionic character, percent, 18
Ionic strength, effect on nucleophilic substitution, 295
Ionizing power of solvents, 296, 297
Ion-pair mechanism of elimination, 748, 752
Ion pairs, 125
  in addition to double bonds, 564
  in allylic rearrangements, 271
  with carbanions, 146
  in elimination reactions, 735, 739, 746
  in Friedel-Crafts alkylation, 411
  in nucleophilic substitution, 259–260, 269, 271
Ion-radicals, 158, 713, 907
  from alkenes, 608
  in Birch reduction, 597
  (*See also* Ketyls)
Iron, in halogenations, 403
  reduction of nitro compounds, 897
Isoborneol, 795
Isobornyl chloride, 750
Isobutane, bond energies of, 25
  bromination of, 531
  chlorination of, 791
  dipole moment, 19
  formation of, 164, 468
  mass spectrometry of, 197
Isobutane, reaction, with carbon atoms, 466
    with ethylene, 602
Isobutene, addition reactions of, 585
  bond angles of, 14*n*.
  formation of, 307, 734
  reaction with carbene, 467
Isobutyl bromide, 744
Isobutyl phenyl ketone, 910
Isobutyl radical, 791
Isocyanates, addition, to enamines, 724
    to isocyanates, 718
  formation of, 335, 341, 342, 591, 781, 816–821, 886 (*see also* 977)
  hydrolysis of, 658
  reaction, with alcohols, 663
    with amines, 672
    with aromatic rings, 416
    with bisulfite ion, 665
    with Grignard reagents, 691
    with phosphorus ylides, 708
  reduction of, 899–900
Isocyanides (*see* Isonitriles)
Isonitriles, addition reactions of, 724–726
  formation of, 300, 334, 361, 778
  hydrogen bonding of, 65
  oxidation of, 886
Isopentane, 601
Isoprene, 2 + 2 cycloadditions of, 639
  in Diels-Alder reaction, 626
  reaction with HCl, 577
Isopropenyl acetate, 323
1-Isopropenyl-4-methyl-1,4-cyclohexadiene, 900
Isopropyl cation, 126
Isopropylmethylcyclohexenes, 730, 735
Isoquinolines, 423
Isoracemization, 448
Iso system in naming, 914
Isothiocyanates, formation of, 335, 342, 512, 673 (*see also* 977)
  hydrolysis of, 658
  reaction, with alcohols, 663
    with amines, 673
    with aromatic rings, 416
    with carbodiimides, 719
    with Grignard reagents, 691
    reduction of, 899–900
Isothiuronium salts, 328
Isotope effects, 213–216
  in aromatic substitution, 377
  in elimination reactions, 737
Isotopically labeled compounds, naming of, 930
Isotopic exchange reactions, 207, 458
Isotopic labeling, mechanistic information from, 206
Isovalent hyperconjugation, 58
Isovaleric acid, 352
I-strain, 234, 286
IUPAC names, 912–913

J (coupling constant), 187, 188
Jacobsen reaction, 436
Japp-Klingemann reaction, 461
Journals, 932–936, 954–955
  abbreviations, 934, 935, 939, 946, 947, 954

Ketals (*see* Acetals)
Ketene, conversion to carbene, 164, 468
Ketene dimers, 636, 723, 766
Ketenes, in acylation of aromatic rings, 413
  addition, of amines, 591
    of carboxylic acids, 587
    of enols, 585
    of ROH, 585
    of RSH, 588
  cycloaddition reactions, 636, 637, 723, 724
  dimerization, 636, 723
  1,3-dipolar addition to, 625
  formation of, 165, 754, 766, 771, 809
  halogenation of, 612
  reaction, with hydrogen halides, 581
    with phosphorus ylides, 708
    with water, 582
  reduction of, 679
Ketenimines, addition of amines, 591
  formation of, 709, 754
Ketimines (*see* Imines)
Keto acid oximes conversion to nitriles, 776
Keto acids, cleavage of, 868
  conversion to acyl halides, 347
  decarbonylation of, 315, 347
  decarboxylation of, 478, 479
  formation of, 336, 357, 365, 415, 482
  rearrangement of, 803
Keto aldehydes, cleavage of, 868
  conversion to hydroxy acids, 909
  formation of, 357, 364, 368, 464, 657, 880
  hydration of, 655
  reaction with hydrazines, 674
Keto alkylidenephosphoranes, 369
Keto amides, 460
Keto-enol tautomerization, 59, 457
Keto epoxides reduction to alkenes, 345
Keto esters, addition to activated olefins, 604
  ambident nucleophiles from, 298, 299
  basic cleavage of, 481
  condensation with phenols, 423
  conversion to enol esters, 472
  decarboxylation of, 479
  dimerization of, 888
  fluorination of, 458
  formation of, 357–359, 364, 366–368, 650, 688, 872
  reaction, with diazonium ions, 460
    with Grignard reagents, 685
    with hydrazines, 674
  reduction of, 680
Keto ether oximes, 776
Keto ethers, formation of, 317
Keto form, in tautomerism, 59–61
Ketones, acylation of, 364–366, 368, 716
  addition to activated olefins, 604
  addition reactions of, mechanism, 651–654
    stereochemistry, 90
  alkylation of, 357, 359, 360, 464
  arylation of, 506
  asymmetric reduction of, 91
  Baeyer-Villiger rearrangement, 822
  bimolecular reduction of, 903
  cleavage of, 435, 482–483, 870
  in complex formation, 69
  condensation, with active hydrogen compounds, 697
    with aldehydes, 695, 697, 701
    with aromatic rings, 421–423
    with esters, 696, 697
    with α-halo esters, 700
    with ketones, 694, 697
    with phosphoranes, 702–709
    with Schiff bases, 695
  conversion, to *gem*-dihalides, 677
    to enol ethers, 317
    to epoxides, 720
    to α-halo ethers and alcohols, 676
    to hydrazones, 461
    to oximes, 675
    to γ,δ-unsaturated ketones, 833
  coupling of, 549, 903
  cycloaddition reactions, 723
  enolization of, 457
  formation of, 303, 306, 307, 323, 325, 346, 357, 359–360, 362–372, 413–415, 418, 420, 424, 428, 438, 456, 458, 464–465, 478–482, 560, 582–584, 586, 600, 605, 606, 619, 656–659, 689, 691, 754, 773–776, 778–779, 798, 801–802, 811, 817, 824, 848, 862–884, 893 (*see also* 978)
  formylation of, 464
  in haloform reaction, 482
  halogenation of, 458
  in Mannich reaction, 670
  optical rotatory dispersion of, 111–116
  oxidation, of alcohols, 863
    to diones, 880
  oxidative cleavage of, 870
  in Passerini reaction, 725
  photolytic cleavage of, 870
  reaction, with alcohols, 661
    with alkenes, 713
    with alkynyl ethers, 714
    with amines, 667
    with ammonia, 666
    with arylhydrazones, 844
    with bisulfite ion, 665

- Ketones, reaction, with cyanide ion, 710
      - and ammonia, 710
    - with diazo alkanes, 810
    - with hydrazine derivatives, 674
    - with hydrazoic acid, 819–821
    - with hydrogen sulfide, 665
    - with ketene, 585
    - with mercaptans, 665
    - with organometallic compounds, 684
    - with oxazolones, 700
    - with water, 655
  - rearrangement of, 801–802, 810, 819, 822
  - reduction, to alcohols, 678
    - of C=O to CH_2, 891–894
  - in reductive alkylation, 663, 668
  - in Reformatsky reaction, 687
  - sulfonation of, 462
  - tautomerism of, 60
  - Willgerodt reaction of, 910
  - (*See also under* Diketones; Unsaturated ketones; etc.)
- Ketonic decarboxylation, 370
- α-Ketophenylacetaldoxime, 899
- β-Keto sulfoxides, 369
- α-Ketotriphenylphosphazines, 657
- Ketoximes (*see* Oximes)
- Ketyls, 158, 682, 713, 903
- Keyword indexes, 938, 940, 953
- Kiliani method, 710
- Kindler modification, 910, 911
- Kinetic acidity, 143
- Kinetically controlled products, 204
- Kinetic requirements for reaction, 202
- Kinetics, mechanistic information from, 208–216
- Kizhner reaction, 893
- Knoevenagel condensation, 693, 697
- Knotted rings, optical activity of, 81
- Kolbe reaction, 557
- Kolbe-Schmitt reaction, 420
- Krebiozen, 180
- Kröhnke reaction, 883
- KWIC indexes, 938, 940, 953

- Lactams, addition to multiple bonds, 590
  - formation of, 337, 338, 724, 820 (*see also* 979)
  - hydrolysis of, 313
  - reduction of, 895
- Lactic acid, 82, 83, 85
- Lactones, condensation with aldehydes and ketones, 696
  - conversion, to hydroxy esters, 322
    - to lactams, 338
  - formation of, 320, 323, 586, 696, 723, 823, 850, 883, 896, 897 (*see also* 979)
- Lactones, hydrolysis of, 310, 312
  - pyrolysis of, 757
  - reaction with cyanide ion, 362
  - reduction of, 896
- Ladenburg benzene, 119, 643
- Landolt-Bornstein's "Zahlenwerte und Funktionen," 944
- Large-angle strain, 120
- LCAO method, 8
- L configuration, 83–88
- Lead dioxide, 611
- Lead tetraacetate, 857*n.*
  - in acyloxylation, 545
  - in bisdecarboxylation of dicarboxylic acids, 879
  - free radicals from, 153
  - in nitrile formation, 676
  - in oxidation, of amines, 866, 889
    - of carboxylic acids, 878
    - of diamines, 876
    - of 1,2-diols, 867–869
    - of phenols, 866
  - reaction, with alcohols, 542, 862
    - with alkenes, 618
    - with amides, 817
    - with carboxylic acids and halide ions, 559
    - with cyclopropanes, 579
    - with quinones, 553
- Lead thiocyanate, 416
- Least motion, principle of, 598
- Leaving groups, effect on ambident nucleophiles, 301
  - in electrophilic substitution, 376, 442, 451
  - in elimination reactions, 745
  - in nucleophilic aliphatic substitution, 290–294
  - in nucleophilic aromatic substitution, 489, 493, 498
  - in rearrangement reactions, 796
- Lederer-Manasse reaction, 422
- Lethargic reactions, 675
- Leuckart reaction, 669
- Leveling effect, 223
- Levo (−) rotation, 72
- Levulinic acid, 657
- Lewis acid-base reactions, 200, 227
- Lewis structures, 15–17
- Light energy, 168
- Limonene, 900
- Linear free-energy relationships, 227, 240, 289, 296
- Literature, chemical, 932–955
- Literature searching, 952–955
- Lithium, in amines, reduction, of acids, 352
      - of aromatic rings, 598
      - of double bonds, 592, 596
  - in ammonia, reaction, with alkyl halides, 354
      - with unsaturated ketones, 360

Lithium, in ammonia, reduction of aromatic rings, 597
  reaction with alkyl halides, 476, 798
Lithium aluminum deuteride, 348
Lithium aluminum hydride, reduction, of acetals, 350
    of acyl halides, 897
    of alcohols, 349
    of aldehydes, 678, 679, 681
    of alkenes, 593
    of alkyl halides, 348
    of amides, 352–353, 895
    of amine oxides, 901
    of amines and quaternary salts, 351
    of anhydrides, 896, 897
    of aryl halides, 440
    of azides, 899–900
    of azoxy compounds, 901
    of carboxylic acids, 894
    of C=N compounds, 682–683
    of dihalides, 770
    of disulfides, 903
    of episulfides, 769
    of epoxides, 350
    of esters, 896
    of ethers, 350
    of hydroperoxides, 901
    of isocyanates, 899–900
    of isonitriles, 725
    of isothiocyanates, 899–900
    of ketones, 91, 678, 679, 681, 893
    of nitriles, 683, 684
    of nitro compounds, 897, 907
    of nitroso compounds, 908
    of ortho esters, 350
    of oximes, 899
    of ozonides, 871
    of peroxides, 902
    of sulfones, 901
    of sulfonyl halides, 900
    of sulfoxides, 901
    of tosylhydrazones, 894
  selectivity, 890–892
Lithium borohydride, 896
Lithium borohydride-lithium hydride, 348
Lithium bromide, 259
Lithium chloride, 745
Lithium diethylamide in aldol condensations, 695
Lithium N-dihydropyridylaluminum hydride, 679
Lithium hydride, 767
Lithium mercury bromide, 445
Lithium nitride, 335
Lithium perchlorate, 259
Lithium triethoxyaluminum hydride, 684
Lithium trimethoxyaluminum hydride, selectivity, 892
Lithium tri-*tert*-butoxyaluminum hydride, 351, 352
  selectivity, 892
Lithium tri-*tert*-butylaluminum hydride, 352
Lone pair size, 12
Lossen rearrangement, 783, 819
Lowest-unoccupied orbitals, 633–636
Lucas test, 343

+*M* and −*M* groups, 231, 232
McFadyen-Stevens rearrangement, 353
Magnesium, reaction, with alkyl halides, 349, 475, 798
    with dihalides, 770
    with dihalocyclopropanes, 644
    with β-halo compounds, 771, 772
  reduction of aldehydes and ketones, 903
Magnesium (I), 857*n*.
Magnesium exchange in Grignard solutions, 151
Magnetically anisotropic groups, 184
Magnetic moment of electrons, 153
Magnetic resonance [*see* Nuclear magnetic resonance (nmr)]
Maleic acid, 96, 97, 101, 565
Maleic acid-iron-tetracarbonyl, 80
Maleic anhydride, 2 + 2 cycloadditions of, 637
  as dienophile, 626, 629–631
  in ene synthesis, 603
  formation of, 875
Maleic anhydride-benzene photoadducts, 637
Maleimide, 637
Malic acid, 253
Malonamide, 340
Malonic acid, dehydration of, 754
  halogenation of, 460
Malonic acid derivatives, bisdecarboxylation of, 879
  decarboxylation of, 478, 479
Malonic acid esters, ambident nucleophiles from, 298
  formation of, 357–358, 366, 585
Malonic ester synthesis, 357, 360, 506
Mandelic acid, 91, 93
Mandelonitrile, 91
Manganese dioxide, 857*n*.
  oxidation, of alcohols, 862
    of amines, 889
    of hydrazones, 867
  reaction with nitriles, 660
Manganese ions in peroxide formation, 545
Manganous chloride, 555
Mannich bases, alkylation with, 361
  formation of, 333, 670–672
  nucleophilic substitution of, 280
  reaction with cyanide ion, 361
  transamination of, 333

Mannich reaction, 424, 670, 710
Markovnikov addition, 576–578
  of acetyl nitrate, 623
  of alkyl halides, 615
  to cyclopropanes, 579
  of hydrogen halides, 580
  of hypohalous acids, 612
  of NOCl, 614
  of RCOOH, 586
  of RH, 602
  of ROH, 585
  of sulfur compounds, 587
  of water, 581, 582
Markovnikov's rule, 576
  in acylation of alkenes, 463
  in double-bond shifts, 453
  in Friedel-Crafts alkylations, 411
  in Grignard rearrangements, 815
  in hydroboration, 599
  in hydrocarboxylation, 609
  in oxidation with palladium chloride, 884
  in Prins reaction, 712
Mass law effect in S_N1 reactions, 257, 295
Mass spectra, 196–198, 207
Mechanical resolution, 93
Mechanisms, types of, 199–202
Meerwein arylation, 552
Meerwein-Ponndorf-Verley reduction, 680, 681
Meisenheimer salts, 489
Menschutkin reaction, 331
Menthyl acetate, 752
Menthyl alcohol, 91
Menthyl chloride, 730, 735
Meprobamate, naming of, 912
Mercaptals, formation of, 588, 665
Mercaptans, addition to multiple bonds, 571, 575, 587, 791
  in alkylation of aromatic rings, 407
  conversion, to amines, 502
    to halides, 504
    to sulfides, 328, 500, 501, 587, 791
    to thiol esters, 329
  in decarbonylation reactions, 560
  desulfurization of, 556
  formation of, 310, 328, 330, 403, 473, 500, 512, 587, 757, 900, 903 (*see also* 980)
  in hydrocarboxylation, 609
  oxidation of, 885, 888
  reaction with aldehydes and ketones, 664
Merck Index, 944
Mercuric acetate, 445
  acyloxylation with, 545
  reaction, with alkenes, 582
    with amines, 861
Mercuric biscobalttetracarbonyl, 642
Mercuric bromide, 444–446
Mercuric chloride, 11
Mercuric fluoride, 342
Mercuric ions in addition to triple bonds, 585, 587
Mercuric nitrate, 445
Mercuric oxide, oxidation, of hydrazones, 867
    of isonitriles, 886
  reaction, with carboxylic acids, 559
    with glyceraldehyde, 83
    with iodohydrins, 799
    with tosylhydrazones, 764
Mercuric sulfate, 400, 582
Mercury, hybridization in, 10
Mercury fulminate, 425
Merged substitution-elimination mechanism, 738
Mesitoic acid, 312, 819
Mesitoic acid esters, 312
Mesitylene, alkylation of, 379
  formation of, 435
  hydroxylation of, 426
Mesitylenesulfonyl chloride, 372
Meso forms, 87, 98
Mesoionic compounds, 54
Mesomeric effect (*see* Resonance effects)
Meta-directing groups, in electrophilic substitution, 382, 386–387
  in nucleophilic substitution, 495
Metalation reactions, 468–470, 473–476
Metal ion complexes, 66–67, 80, 583
Metallocenes, 42, 44, 67
  formation of, 474
  optical activity of, 80
  (*See also* Ferrocenes)
Methane, bond angles of, 12
  bond energy of, 25
  chlorination of, 533, 534
  exchange of hydrogens, 594
  formation of, 477
  nitration of, 547
  reaction with carbene, 164
Methanesulfonic acid, 310
1,6-Methanocyclodecapentaene, 54
1,6-Methanocyclodecapentaene-2-carboxylic acid, 54*n*.
Methanol, bond angles of, 24
  in clathrate compounds, 70
  electronic spectrum of, 171
  formation of, 759
  reaction with triphenylmethyl chloride, 261
Methoxide ions, in Favorskii rearrangement, 806
  as nucleophiles, 215, 489, 496
m-Methoxyaniline, 493
4-Methoxybenzyl alcohol, 261
4-Methoxybenzyl azide, 261
4-Methoxybenzyl chloride, 261
1-Methoxy-1,4-cyclohexadiene, 597
4-Methoxycyclohexyl acetate, 265
2-Methoxycyclohexylmercury chloride, 443, 444

4-Methoxycyclohexyl tosylate, 265
2′-Methoxy-2-nitro-6-carboxybiphenyl, 78
2-(*p*-Methoxyphenyl)ethyl bromide, 267
1-Methoxy-2,2,3,3-tetramethylcyclopropanol, 806
Methoxytriphenylmethane, 261
p-Methylacetophenone, 409
4-Methyl-3-acetoxycyclohexene, 271
Methylacetylene, 101
Methylamine, 24
m-(3-Methylaminopropyl)chlorobenzene, 502
N-Methylaniline, chlorination of, 405
  formation of, 430
  rearrangement of, 432
Methylation of aromatic compounds, 509
N-Methyl-5-azacyclononanone, 121
Methylbenzenesulfonic acids, 439
Methyl benzoate, 50
2-Methylbenzophenone, 433
2-Methylbenzyltrimethylammonium ions, 518
10-Methylbicyclo[5.3.1]undec-1(10)-en-11-one, 122
α-Methyl-β-bromocrotonic acid, 774
3-Methyl-1,2-butadiene, 79
2-Methylbutanal, 90
2-Methylbutane, 467
2-Methyl-2-butanol, 581, 582
Methylbutanols, 788, 789
3-Methylbutanone, 893
2-Methyl-1-butene, formation of, 467
  oxymercuration of, 582
2-Methyl-2-butene, formation of, 740, 795
  hydroboration of, 599
3-Methyl-1-butene, formation of, 740, 788
  rearrangement of, 581
Methylbutenes, formation of, 750, 752
2-Methyl-3-buten-2-ol, 274
3-Methyl-2-buten-1-ol, 274
3-Methyl-2-butyl acetate, 752
2-Methyl-5-*tert*-butylbenzophenone, 433
3-Methyl-2-butyl chlorosulfite, 269
α-Methylbutyrophenone, 446
1-Methyl-4-carbomethoxypyridinium ion, 297
1-Methyl-4-chloro-4-benzoylpiperidine, 808
1-Methyl-1,6-cyclodecanediol, 121, 789
6-Methylcyclodecanone, 121, 789
Methylcyclohexane, 105
Methylcyclohexenes, 752
N-(4-Methyl-2-cyclohexenyl)piperidine, 271
Methylcyclopentane, 109
3-Methyl-1,2-cyclopentanedione, 190
1-Methylcyclopentanol, 800
1-Methylcyclopentene, 800
4-Methylcyclopentene, 578
4-Methylcyclopentene oxide, 578
Methylcyclopropane, 466, 579
(1-Methylcyclopropyl)carbinyl methanesulfonate, 140
2-Methylcyclopropyl xanthate, 752
N-Methyl-2,6-di-*tert*-butylpyridinium iodide, 124
Methylenebis(triphenylphosphonium) ion, 703
Methylenecycloalkanes, addition reactions of, 577
Methylenecyclobutane, 799
Methylenecyclohexane, 704
Methylenecyclohexenes, 627
Methylenecyclopropanes, 645
3-Methylene-17-hydroxyandosterane epoxide, 721
Methylenes (*see* Carbenes)
6-Methylene-1,3,5-trimethyl-1-dimethylaminomethyl-2,4-cyclohexadiene, 518
3-Methylethylcyclopentane, 99
3-Methyl-4-ethyl-3-heptene, 95
4-Methyl-1-ethylidenylcyclohexane, 79
Methyl ethyl ketone (*see* Butanone)
3-Methyl-1-ethyl-3-phospholene-1-oxide, 718
3-Methyl-2-ethyltetrahydrofuran, 542
Methylglyoxal, 872
2-Methylheptane, 70
3-Methyl-3-heptene, 95
3-Methyl-1,5-hexadiene, 834
4-Methyl-2-hexene, 96
3-Methylindole, 647
Methyllithium, reaction, with enol acetates, 359
  with phosphonium salts, 703
Methylmagnesium bromide in Zerewittenoff process, 471
Methylmagnesium halides reaction with trinitrobenzene, 606
Methylmagnesium iodide reaction with hexafluorobenzene, 506
Methyl mercaptan, 24
2-Methylnaphthalene, 876
2-Methyl-2-nitro-1-(*p*-nitrophenyl)propane, 301
2-Methyloctane, 70
Methyl 2-octyl ether, 262
Methyl oleate, 873
4-Methyl-7-oxabicyclo[2.2.1]-2-heptene-5,6-dicarboxylic anhydride, 631
Methylpentafluorobenzene, 506
3-Methyl-2,2′,4,4′,6-pentanitrobiphenyl, 68
Methylpentenes, 599, 873, 874
Methylpentenones, 173
4-Methyl-2-*tert*-pentylphenol, 409
(2-Methyl-3-pentyl)trimethyl ammonium ion, 741
Methyl phenethyl ether, 388
3-Methyl-3-phenylbutanal, 790
2-Methyl-4-phenylbutanoamide, 910
1-Methyl-4-phenyl-4-carboxypiperidine, 808
5-Methyl-3-phenyl-2-hexanone, 237
2-Methyl-1-phenylpropane, 790

(2-Methyl-2-phenylpropyl)(2-methoxycyclohexyl)mercury, 443, 444
2-Methylpiperidine, 758
1-(2-Methyl-1-propenyl)cyclohexene, 841
Methyl propiolate, 50
2-Methylpyridines, acylation of, 369
  alkylation of, 358
  condensation with aldehydes and ketones, 697
  Mannich reaction of, 670
4-Methylquinoline, 647
Methyl radical, 153, 155
Methyl sulfate, 317
Methylsulfinyl carbanion, reaction, with alkynes, 361
    with aromatic compounds, 509
    with esters, 369
N-Methyltetrahydroquinoline, 502
Methyl 2,4,6-tri-*tert*-butylbenzoate, 312
2-Methyl-4,4,4-triphenyl-2-chlorobutane, 773
Methyltriphenylphosphonium bromide, 703
1-Methyl-2-vinylcyclopropane, 841
Michael reaction, 568, 604, 698
  reversal, 767
  in Skraup synthesis, 423
Michael-type reactions, 465, 568, 569, 574, 577, 737
Michael-type substrates, 2 + 2 cycloadditions of, 636, 637
  Diels-Alder reactions of, 626
  epoxidation of, 620
  reaction, with active hydrogen compounds, 604
    with amines, 590
    with ammonia, 590
    with hydrogen cyanide, 610
    with hydrogen halides, 580
    with organometallic compounds, 604
    with phosphines, 703
    with ROH compounds, 585
    with RSH compounds, 588
    with water, 582
    with ylides, 649
Microscopic reversibility, 204
Microwave spectra, 175, 181, 182
Migration (*see* Rearrangements)
Migratory aptitudes, 787
Miltown, naming of, 912
Mirror plane, 73
Mixed S_N1 and S_N2 mechanisms, 261, 297
Modes of vibration, 178
Molar rotation, 73
Molecularity of reactions, 208
Molecular orbital method, 8, 29–34
  free valence in, 56
Molozonides, 874
Monographs, 947–949
Monopersuccinic acid, 617
Monothiophthalimide, 416
Morphine, 92
Multiple valence, 9

Nametkin rearrangement, 796
Naming, of organic compounds, 912–931
  of stereoisomers, 72, 83, 88, 94, 100
Naphthalene, 46
  alkylation of, 408, 509
  annellation in, 40
  arylation of, 412
  canonical forms, 39
  in Diels-Alder reaction, 627
  formation of, 422, 861
  formylation of, 418
  free valence in, 56
  orientation in, 390, 391
  oxidation of, 875
  reaction with radicals, 558
  resonance energy of, 39
  sulfonation of, 383
Naphthalenesulfonic acids, 383
1-Naphthoic acid, 206, 515, 876
Naphthols, 499, 501, 502
Naphthylamines, 499, 502
Naphthylcarbenes, 162
2-Naphthyl cyanide, 515
n-donors in complexes, 66, 68, 69
Near infrared spectra, 175
Neber rearrangement, 815
Nef reaction, 659
Neighboring-group mechanism, 263–268, 618
  at carbonyl carbon, 277
  in elimination reactions, 733
Neighboring-group participation, by alkyl groups, 131, 136, 267
  by aryl groups, 131, 132, 266
  by double bonds, 131, 267
  free radical, 525
Neighboring groups, 266–268
  migration of, 785, 813
Neomenthyl chloride, 730
Neon, 70
Neopentylbenzene, 434
Neopentyl bromide, 783
Neopentyl cation, 785, 786
Neopentyl chloride, 750, 795
Neopentyl compounds, rearrangement of, 783, 785, 790, 791, 794–795
Neophyl compounds, rearrangement of, 783, 790, 794–795
"Newer Methods of Preparative Organic Chemistry," 951
Newman projection formulas, 102
Nickel, aromatization catalyst, 860
  reaction with nitriles and water, 660
  (*See also* Raney nickel)

Nickel acetate, 821
Nickel carbonyl, 649
  in carbalkoxylation of aryl iodides, 507
  in hydrocarboxylation, 608
Nickel compounds in trimerization of alkynes, 642
Nickel peroxide, 876
Nitration, of alkanes, 547
  of aromatic rings, 382, 387, 388, 390, 395, 396
N-Nitration, 486
Nitrene, reaction with butadiene, 645
Nitrenes, 162, 782
  insertion reactions of, 467
  in rearrangement reactions, 782–783, 816–818
Nitric acid, oxidation, of ketones, 870
    of sulfur compounds, 885
  Raman spectrum of, 398
  reaction, with alcohols, 326
    with alkanes, 547
    with alkenes and HF, 614
    with anhydrides, 327
    with aromatic rings, 396
  (*See also* Nitration)
Nitric acid anhydrides, formation of, 327
Nitrile oxides, 886, 901
Nitriles, acylation of, 364, 368
  addition to alkenes, 604, 607
  alcoholysis of, 664
  alkylation of, 357
  condensation, with aldehydes and ketones, 697
    with nitriles, 709
  coupling of, 549
  formation of, 300, 357, 358, 361, 425, 477, 506, 554, 610, 675, 700, 719, 776–778, 817, 866, 886, 895, 901 (*see also* 980)
  hydrolysis of, 660
  in Mannich reaction, 670
  reaction, wth aldehydes, 697, 717
    with ammonia or amines, 673
    with aromatic rings, 424
    with carbonium ions, 715
    with carboxylic acids, 716
    with free radicals, 528
    with Grignard reagents, 691
    with zinc and halo esters, 688
  reduction of, 683, 900
  trimerization of, 720
Nitrite ions, as ambident nucleophiles, 299, 300
  reaction, with alkyl halides, 341
    with diazonium salts, 554
Nitro acetates, formation of, 623
Nitro acids, decarboxylation of, 478, 479
Nitro alcohols, formation of, 623, 702
Nitro aldehydes, formation of, 623
Nitro alkyl nitrates, 623
Nitro alkyl nitrites, 622
Nitroamines, 430
N-Nitroaniline, 430
o-Nitroanilinium ion, 224
Nitrobarbituric acid, 547
o-Nitrobenzamide, 277
Nitrobenzene, alkylation of, 408, 509
  dipole moment, 19
  nitration of, 382
  resonance in, 232
  in Skraup synthesis, 423
p-Nitrobenzyl compounds, 301
Nitrobromobenzene, 490, 496
1-Nitro-2-chloro alkenes, 614
Nitrochlorobenzenes, 496
Nitro compounds, addition to activated olefins, 604
  alkylation of, 357, 408, 509, 553
  in complex formation, 67
  condensation with aldehydes and ketones, 697, 702
  conversion, to amines, 502
    to dinitro compounds, 341
    to ethers, 500
    to halides, 504
  formation of, 300, 341, 357, 396, 430, 434, 439, 478, 486, 509, 547, 554, 614, 622, 885 (*see also* 980)
  halogenation of, 460
  hydrolysis of, 499, 659
  in Mannich reaction, 670
  methylation of, 509
  reaction, with cyanide ions, 514
    with diazonium ions, 460
    with Grignard reagents, 606
  reduction of, 505, 897, 898, 901, 905–908
  reductive alkylation of, 670
  in Skraup synthesis, 423
  tautomerism of, 62
2-Nitroethanol, 702
Nitro form in tautomerism, 62
Nitrogen as leaving group, 290, 491
Nitrogen atom, bonding of, 10
Nitrogen dioxide, 548
Nitrogen-nitrogen double bonds, in Diels-Alder reaction, 627
  formation of, 780, 867
  isomerism of, 95
Nitrogen-oxygen double bonds in Diels-Alder reaction, 627
Nitrogen trichloride, 400
Nitrogen ylides (*see* Ylides, nitrogen)
Nitro group as leaving group, 498
Nitro ketones, formation of, 623
Nitromethane, condensation, with benzaldehyde, 697
    with formaldehyde, 702
  reaction, with acetylene, 606
    with carboxylic acids, 819

Nitromethylanilines, 430
N-Nitro-N-methyl-*p*-fluoroaniline, 431
2-Nitronaphthalene, 206, 515
N-Nitronaphthylamines, 430
Nitronic esters from alkylation of nitropropane, 301
Nitronium ions as nitrating agents, 393, 397, 398
2-(*o*-Nitrophenoxy)ethanesulfinic acid, 520
O-(*o*-Nitrophenoxy)sulfinic acid, 519
p-Nitrophenylhydrazones, 674
Nitropropane reaction with aldehydes, 676
2-Nitropropane carbanion, 301
1-Nitropropene, 606
Nitrosation, at aliphatic carbon, 462
    of aromatic rings, 397, 398
N-Nitrosation, 486
N-Nitroso-N-alkyl amides, 780
N-Nitroso-N-alkyl-4-amino-4-methyl-2-pentanoates, 780
N-Nitroso-N-alkylureas, 780
N-Nitroso-N-alkylurethanes, 780
N-Nitroso amides in arylation reactions, 551, 552
Nitrosoamines, 430
o-Nitrosobenzamides, 516
Nitrosobenzene, 907
Nitroso compounds, conversion to imines, 462
  formation of, 398, 430, 436, 462, 613, 623, 867, 884 (*see also* 981)
  oxidation to nitro compounds, 397, 885
  reaction, with amines, 908
    with hydroxylamines, 907
    with phosphorus ylides, 708
  reduction of, 898, 907, 908
  in reduction of nitro compounds, 898
  reductive alkylation of, 670
  tautomerism of, 61
N-Nitroso compounds, conversion to diazoalkanes, 780
  formation of, 486
  reduction of, 899
N-Nitrosodimethylamine, 194
p-Nitrosodimethylaniline, 883
N-Nitroso-N-methyl-*p*-toluenesulfonamides, 780
N-Nitroso-N-methylurethane, 780
Nitroso nitro compounds, 623
Nitrosonium ion, 399, 431, 485
Nitroso-oxime tautomerism, 61
p-Nitrosophenols, 436
Nitrosyl chloride, 613, 850
Nitrotetrafluoroanilines, 495
Nitrotoluenes, 19, 388
N-Nitrotoluidine, 430
Nitrourea, 897
Nitrous acid, reaction, with active hydrogen compounds, 462
    with alcohols, 326, 327

Nitrous acid, reaction, with amides, 314, 486
    with amines, 484, 486, 784, 786, 799
    with amino alcohols, 799
    with aromatic rings, 397–400
    with cyclic amines, 799
    with hydrazides, 818
    with hydrazines, 485
    with *p*-hydroxy acids, 436
    with phosphazines, 657
Nitryl chloride, 614
Nitryl halides, 397, 614
^{14}N nmr, 193
No-bond resonance (*see* Hyperconjugation)
Nodes, of atomic orbitals, 5
  in benzene, 29
  in butadiene, 31
  in ethylene, 14
  of π orbitals, 13–15
Nomenclature (*see* Naming)
Nonafluorocyclohexanes, 611
Nonalternant hydrocarbons, 46, 47, 49
Nonbenzenoid aromatic compounds, 40–46, 48–55
Nonbonded interactions, 117, 119–124
Nonchair conformation, 105
Nonclassical carbanions, 146
Nonclassical carbonium ions, 130–140, 266–268, 410
4-Nonene, 873
Nonsuperimposability on mirror images, 71–81, 98, 104, 107
Norbornadiene, 628
7-Norbornadienyl cation, 135
Norbornane, 106, 529, 922, 924
Norbornene, epoxidation of, 620
  formation of, 122, 732, 739
  reaction, with benzyne, 637
    with dichlorocarbene, 648
    with mercaptans, 790
5-Norbornene-2-boronic acid, 450
5-Norbornene-1-carboxylic acid, 629
7-Norbornenyl cation, 130
7-Norbornenyl tosylate, 267
2-Norborneol, 100, 122
2-Norbornyl acetate, 136
Norbornyl bromide, 732, 738
2-Norbornyl brosylate and tosylate, 131, 136, 137, 139
2-Norbornyl cation, 130, 131, 136, 138
Norbornyl sulfide, 791
Norbornyl systems, rearrangement of, 783
7-Norbornyl tosylate, 267
2-Norbornyltrimethylammonium hydroxide, 759
Norcaradienes, 647, 836, 844
Norcarane, 922, 924
Norepinephrine, 922
Nor names, 922, 923
Norpinane, 922

Nortricyclylmercuric chloride, 450
n-π^* transitions, 172
n-σ^* transitions, 171
Nuclear magnetic double resonance, 187
Nuclear magnetic resonance (nmr), 182–195
  and aromaticity, 52, 184, 193
  of carbonium ions, 127, 135
  to measure resonance effects, 244
Nuclear quadrupole resonance, 188, 195
Nuclear spin, 182
Nucleophile, definition of, 199
Nucleophilic addition to multiple bonds, 200, 567–569, 573, 652
  orientation and reactivity in, 573–575, 577
Nucleophilic catalysis, 277, 309, 310, 320
Nucleophilic free radicals, 528, 531, 575
Nucleophilicity, 287–290, 499
Nucleophilic substitution, 200
  aliphatic, 251–375
  at aliphatic trigonal carbon, 274
  at allylic carbon, 270
  aromatic, 488–520
  versus elimination, 728, 734, 738, 744–747
  mechanisms, 251–280, 488–494
  reactivity, 281–302, 494–498
  at vinyl carbon, 278

O-acylation versus C-acylation, 298
O-alkylation versus C-alkylation, 298, 300, 301
n-Octadecyl bromide, 746
n-Octadecyl tosylate, 746
Octafluorocyclohexanes, 611
Octahedral compounds, isomerism of, 76, 100
Octalone, 605
Octane, 70
Octanediols, 789
2-Octanol, 260, 262
Octant rule, 112, 115
1-Octene, 789
2-Octene, 181
4-Octenes, 712
2-Octyl acetate, 263
2-Octyl azide, 260, 262
2-Octyl brosylate, 262
2-Octyl iodide, 255
2-Octyl methanesulfonate, 260, 262
2-Octyl tosylate, 262
13(18)-Oleanene, 796
Olefins (*see* Alkenes)
One-stage mechanism of nucleophilic aromatic substitution, 494
Oppenauer oxidation, 863, 865
Optical activity, 71–94
  and absolute configuration, 82
  of allenes and cumulenes, 78
  of amines, 75
Optical activity, asymmetric synthesis, 90
  of biphenyls, 76
  cause of, 86
  of coordination compounds, 75, 76
  of cyclic compounds, 98, 100
  dependence on wave length, 110–116
  kinds of molecules displaying, 73–81
  methods of resolution, 92
Optical comparison for determining absolute configuration, 85
Optical isomerism, 71–94
  of cyclic compounds, 98
Optical rotatory dispersion (ord), 110–116
Orbitals, antibonding, 8–9, 13, 31, 633–636
    in alternant and nonalternant hydrocarbons, 46
  atomic, 3–8
    linear combination of, 8
  bonding, 8, 13–15, 29–34, 633–636, 839–841
    in alternant and nonalternant hydrocarbons, 46
  d and *f*, 6, 145
  hybrid, 10–13
  molecular, 8–15
  nonbonding, 47
  p, 5–8, 10
  π, 13–15
    in allyl cation and radical, 34
    in alternant and nonalternant hydrocarbons, 47
    in benzene, 29
    in complexes, 67
    in conjugated dienes, 31
    highest-occupied, 633–636, 839–841
    in hyperconjugation, 57
    lowest-unoccupied, 633–636
    in vinyl chloride, 33
  π^*, 13
  s, 5–8
  σ, 8, 11, 13–15
    in double and triple bonds, 13–15
    in hyperconjugation, 57
    in small rings, 117
  σ^*, 8
  sp, 11, 14, 78
  sp^2, 11, 13
  sp^3, 12, 117
Orbital symmetry, conservation of, 633–636, 639, 641, 837*n*., 839–841
Order of a reaction, 208, 212, 213
"Organic Reaction Mechanisms," 947
Organic Syntheses, 950
  references, ground rules, 249
Organoaluminum compounds, 471, 473, 474
Organoantimony compounds, 474, 476
Organoberyllium compounds, 473, 474, 476
Organobismuth compounds, 473, 474
Organoboron compounds (*see* Boranes)

Organocadmium compounds, formation of, 473, 474
  hydrolysis of, 471
  reaction with acid derivatives, 362, 363
Organocalcium compounds, 689
Organocesium compounds, 148
Organocobalt compounds, 474
Organogallium compounds, 471, 473
Organogermanium compounds, 474
Organogold compounds, 474
Organolead compounds, 474
Organolithium compounds, addition to alkenes, 650
  bonding in, 148
  conversion to ketones, 363, 689
  coupling of, 556
  exchange with alkyl halides, 142
  formation of, 473, 475, 476, 650
  hydrolysis of, 440, 471
  in metalation reactions, 469
  pyrolysis of, 767
  reaction, with aldehydes, 685
    with alkyl halides, 476
    with arenes, 509
    with carbon dioxide, 689
    with carbon monoxide, 689
    with ethers, 755, 827
    with fluorobenzenes, 506
    with imines, 690
    with ketones, 604, 685, 686
    with nitrogen heterocycles, 509
    with unsaturated esters and ketones, 604
Organomagnesium compounds, exchange with organomercury compounds, 143
  formation of, 473
  structure of, 149–151
  (*See also* Grignard reagents)
Organomercury compounds, exchange with organomagnesium compounds, 143
  formation of, 474, 476
  hydrolysis of, 471
  optically active, 445
  reaction, with diazonium salts, 441
    with metals, 473
  reduction of, 471
Organometallic compounds, addition to alkenes, 650
  conversion to free radicals, 153
  coupling reactions, 353–356, 362–364, 555
  formation of, 468–470, 473–476, 650, 815 (*see also* 981)
  hydrolysis of, 440
  in metalation reactions, 468–470
  reaction, with acid derivatives, 362–364, 688
    with acids, 470
    with aldehydes, 684
    with carbon dioxide, 689
    with halogens, 473
    with ketones, 684
    with metal halides, 474
    with metals, 473
    with oxygen, 472
  structure of, 142, 148–151
  (*See also* Grignard reagents)
Organoplatinum compounds, 474
Organopotassium compounds, bonding in, 148
  hydrolysis of, 471
  isolation of, 473
  in metalation reactions, 469
  pyrolysis of, 768
  reaction, with acetophenone, 685
    with halides, 354
Organorubidium compounds, 148
Organosilver compounds, 474
Organosodium compounds, bonding in, 148
  formation of, 473, 476
  hydrolysis of, 471
  isolation of, 473
  in metalation reactions, 469
  pyrolysis of, 768
  reaction, with acetophenone, 685
    with aryl iodides, 508
    with carbon dioxide, 689
    with ethers, 755
    with halides, 354
Organotellurium compounds, 329, 473
Organotin compounds, 473, 474, 476
Organotin hydrides, 348, 351
Organozinc compounds, formation of, 473, 474, 476
  hydrolysis of, 471
  reaction, with acyl halides, 362
    with aldehydes and ketones, 685
    with boron trichloride, 474
    with diazonium ions, 441
    with halides, 354
Ortho effect, 389–390
Ortho esters, conversion to carboxylic acids or esters, 306
  formation of, 316, 318, 663, 664, 846 (*see also* 981)
  reaction, with cyanide ion, 361
    with Grignard reagents, 355
  reduction of, 350
  transetherification of, 318
Orthoformates, formation of, 663
  in formylation of aromatic rings, 419
Ortho-para directing groups, in electrophilic substitution, 382, 385–387
  in nucleophilic substitution, 495
Ortho-para ratio, 387
Ortho thioesters, formation of, 665
Orton rearrangement, 431
Osazones, formation of, 674
Osmic esters, 617

Osmium tetroxide, 616
Oxalic acid, 315
Oxalyl bromide, 364
Oxalyl chloride, in carboxylation of aromatic rings, 420
  in chlorinations, 533
  conversion to acyl isocyanates, 341
Oxalyl halides reaction with carboxylic acids, 347
Oxetanes, formation of, 723
  planarity of, 109
Oxidations, 853–890, 908–911
  of boranes, 600
  of carbanions, 152
  of CH_3 to CHO, 850, 880
  definition of, 853
  of radicals, 157
  of nitro compound salts, 341
  tables of oxidation reactions, 858
  (*See also* Oxygen)
Oxidative cleavage, 867–879
Oxidative coupling, 887–889
Oxidative decarboxylation, 559, 868, 878–879
Oxidative nitrosation, 397
1,6-Oxidocyclodecapentaene, 54
Oxime esters, conversion to nitriles, 776
  rearrangement of, 822
Oxime ethers, conversion to nitriles, 776
  formation of, 317, 327, 586
  reaction with Grignard reagents, 690
Oximes, addition to double bonds, 586
  alkylation of, 327
  bromination of, 536
  conversion, to nitriles, 776–777
    to oxime ethers, 317
  formation of, 237, 462, 614, 675, 850, 884, 901 (*see also* 982)
  geometrical isomerism of, 95
  hydrolysis of, 657
  oxidation to nitro compounds, 885
  reaction, with Grignard reagents, 690
    with hydrogen cyanide, 711
  rearrangement of, 690, 784, 821
  reduction of, 683, 899
  tautomerism of, 61
Oxime tosylates, fragmentation of, 777
  rearrangement of, 815
α-Oximino acids, 700
Oxiranes (*see* Epoxides)
Oxirenes, 621
3-(2-Oxocyclohexyl)diazopropane, 811
Oxonium salts, cleavage of, 345
7-Oxo-2-norbornyl cation, 138
Oxo process, 610
4-Oxo-2,2,6,6-tetramethylpiperidine-1-oxide free radical, 154
Oxy-Cope rearrangement, 835
Oxygen, addition to dienes, 621
Oxygen, in aromatization, 861
  in epoxidation of alkenes, 621
  oxidation, of alcohols, 870
    of hydrazines, 867
    of ozonides, 871
    of phenols, 866
    of susceptible C—H bonds, 543
  reaction, with alkenes and N_2O_4, 623
    with organometallic compounds, 471
  (*See also* Autoxidation)
Oxygen atom, bonding of, 10
Oxygen difluoride, 612, 884
Oxygen molecule, electronic structure of, 16
Oxymercuration, 582
Ozone, 857*n.*
  preparation of, 874
  reaction, with alkenes, 871–874
    with alkynes, 872
    with arenes, 39, 872
    with isonitriles, 886
Ozonides, 871–874
Ozonolysis, 871–874

Palladium, in aromatization, 860
  in decarbonylation, 435, 560
  in reduction, of double bonds, 593
    of tosylates, 505
Palladium-on-barium sulfate, 351
Palladium-on-charcoal, 349, 592, 900
Palladium chloride, in hydrocarboxylation, 608
  in oxidation of alkenes, 883
  reaction with alkenes and CO, 616
Papaverine, 423
Paper chromatography for resolution, 93
Para-Claisen rearrangement, 830, 831
[10]Paracyclophane, 185
[10]Paracyclophane-12-carboxylic acid, 80
Paracyclophanes, 80, 904
Para-directing groups in nucleophilic substitution, 495
Paraffins (*see* Alkanes)
Paraldehyde, 717
Paramagnetism of free radicals, 153
Partial bond fixation, 39
Partial rate factors, 391, 394, 530
Partition factor in aromatic substitution, 378
Partitioning effects, 378, 491
Partly-eclipsed conformation, 104
Passerini reaction, 725
Patents, 936, 939
Pauli exclusion principle, 7
Pauling electronegativity scale, 17
Pechmann reaction, 423
Pentachloroaniline, 498
Pentachloroanisole, 498
Pentachlorocyclopentadienyl cation, 50

3,5-Pentacosamethylene-1,2-benzoquinone, catena compound of, 906
3,5-Pentacosamethylene-4[(13-oxopentacosamethylene)amino]-1,2-benzoquinone, 906
3,5-Pentacosamethylene-4[(13-oxopentacosamethylene)amino]-1,2-dihydroxybenzene, 906
Pentacyclo[4.2.2.0^{2,5}.0^{3,8}.0^{4,7}]decane, 118
Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane, 118
Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane, 118
1,3-Pentadiene, 639
2,3-Pentadiene, 79
Pentadienes, resonance energy of, 32
Pentaerythritol, 702
Pentafluoronitrobenzene, 495
2,3,4,5,6-Pentahydroxyhexanal, 88
Pentalenes, 44
Pentalenyl dianion, 46
Pentamethylbenzenesulfonic acid, 437
Pentamethylbenzoyl cation, 129
2,3,3,4,4-Pentamethyl-2-chloropentane, 773
Pentane, 164
1,3-Pentanedione, 893
Pentanes, bond energy of, 26
2,3,4-Pentanetriol, 88
3-Pentanol, 343
3-Pentanone oxime tosylate, 822
Pentaphenylcyclopentadienyl cation, 50
Pentaphenylethyl cation, 136
Pentasulfides, 330
2-Pentene, 742, 873
3-Penten-2-one, 605
2-Pentyl compounds conversion to olefins, 741, 742
Peracetic acid, in Baeyer-Villiger reaction, 620
  in epoxidation of alkenes, 619
  in iodinations, 405
  in oxidation, of acetals, 865
    of amines, 885
    of azobenzenes, 886
  reaction with alkenes and iodine, 618
Peracids, formation of, 326
  oxidation of nitrogen compounds, 886
Perbenzoic acid, in epoxidation of alkenes, 618
  reaction with ketones, 822
Percent ionic character, determination of, 195
Perchloric acid, 218, 327
Perchlorocyclopentadiene, 627*n.*, 633
Peresters, in acyloxylation, 545
  formation of, 326
  reaction with Grignard reagents, 472
  rearrangement of, 824
Perfluoroacetic acid, 307
peri as prefix, 88
Periodic acid, oxidation, of alkenes, 875
    of diols, 867–869
Periodic acid, oxidation, of phenols, 866
Perkin reaction, 654, 693, 698
Perlauric acid, 578, 620
Permanganate, 857*n.*
  hydroxylation with, 208, 616
  oxidation, of alcohols, 862
    of aldehydes, 539, 541
    of alkanes, 538
    of alkenes, 208, 616, 875
    of amines, 885
    of arene side chains, 876
    of diols, 868
    of ketones, 870
    of sulfur compounds, 885, 887
  reaction, with naphthoquinones, 852
    with nitro compounds, 659
Permuterm index, 937
Peroxides, addition to alkenes, 587
  catalysts, in addition to multiple bonds, 580, 606, 607, 615
    in anti-Markovnikov addition, 580
    in coupling reactions, 549
    in Prins reaction, 713
  cleavage of, 521
  in decarbonylations, 560
  formation of, 325, 545, 621
  reaction, with aromatic compounds, 426, 427, 553
    with enolate ions, 472
    with ketones, 823
  reduction of, 902
Peroxydisulfate ion, 539, 865
Peroxy radicals, 544
Peroxytrifluoroacetic acid, in epoxidation of alkenes, 619
  reaction, with aromatic rings, 426
    with 5,5-diphenylcyclooctyl tosylate, 790
    with ketones, 823
    with octene, 789
    with oximes, 885
Perpendicular disymmetric planes, 76
Phenacyl bromides, 867
Phenalene, 39
Phenanthrene, alkylation of, 509
  canonical forms, 39
  in Diels-Alder reaction, 627
  reaction with maleic anhydride, 637
  reduction of, 597
  resonance energy, 39
Phenol, deuteration of, 396
  dipole moment of, 19
Phenolate ions, as ambident nucleophiles, 300, 301
  oxidation of, 855
Phenol-dienone rearrangement, 802
Phenolic esters, rearrangement of, 428
  reduction of, 505
Phenolic ethers, rearrangement of, 429

Phenolic ethers, reduction of, 505
Phenol-keto tautomerism, 61
Phenols, acylation of, 413, 414
  addition to multiple bonds, 584
  alkylation of, 408, 409, 411
  aminomethylation of, 424
  carboxylation of, 420
  in complex formation, 67
  condensation with aldehydes and ketones, 422
  conversion, to aryl halides, 504
    to aryl sulfides, 501
    to coumarins, 423
    to cyclodienones, 802
    to ethers, 300, 316–318, 500
    to phenolic esters, 319–323
  diazonium coupling of, 399
  formation of, 307, 310, 327, 344, 355, 426, 428, 429, 472, 499–500, 511, 512, 519, 538, 679, 802, 830, 851, 877–878 (*see also* 982)
  formylation of, 417–420
  haloalkylation of, 424
  halogenation of, 403, 405
  in imidate formation, 849
  introduction of diazonium groups in, 399
  nitration of, 397
  nitrosation of, 398
  oxidation of, 539, 865
  reaction, with nitriles, 425
    with sulfonic acid derivatives, 373
  reduction of, 505, 597
  tautomerism of, 61
Phenone system in naming, 915
Phenonium ion, 130–134, 266, 410
Phenoxathiin, 403
Phenoxide ions, alkylation of, 301
α-Phenoxylbenzyllithium, 163
Phenoxymagnesium halides, 419
Phenyl, as neighboring group, 132, 266
Phenylacetaldehyde, 880
Phenylacetophenone, 787
2-Phenyl-2-acetoxy-1-nitrocyclohexane, 736
Phenylacetylene, 650
6-Phenylamino-2*H*-azepine, 818
1-Phenyl-1-*p*-anisyl-2-bromoethylene, 812*n*.
Phenyl azide, 623, 818
Phenylazotriphenylmethane, 551
Phenyl benzyl ether, 429
1-Phenyl-1,3-butadiene, 577
1-Phenylbutan-1,3-dione, 893*n*.
4-Phenylbutanoic acid, 415
4-Phenyl-3-butenal, 422
Phenylbutenes, 603, 833
2-(3-Phenyl-2-butenyl)succinic anhydride, 603
3-Phenyl-2-butyl acetate, 132
3-Phenyl-2-butyl cation, 134
Phenyl butyl ethers, 429
3-Phenyl-2-butyl tosylate, 132
2-Phenyl-3-carbaroxypropionic acids, 428
Phenylcarbene, 163, 326
Phenyl cation, 129
Phenylchloropropanones, 804
2-Phenylcyclohexyl tosylate, 732
1-Phenylcyclopentene, 280
2-Phenylcyclopentyl tosylate, 732
Phenylcyclopropanone, 806
Phenylene anion, cation, and radical, 40
p-Phenylenediamine, 865
2-Phenylethanol, 350, 679
1-Phenylethylamine, 783
Phenylethyl bromide, 354
  elimination reactions of, 736, 738
  pyrolysis of, 750
Phenylethyl cation, 130, 132, 134
Phenylethyl chloride, 260, 354
(2-Phenylethyl)ethyldimethylammonium hydroxide, 760
α-Phenylethyl phenyl ether, 260
2-Phenylethyl tosylate, 132
2-Phenylethyltrimethylammonium ion, 737
9-Phenylfluorene, 412
Phenylhydrazides, formation of, 338
Phenylhydrazine, reaction, with aldehydes and ketones, 674
    with dihalides, 770
    with esters, 338
Phenylhydrazones, formation of, 674
  reaction with Grignard reagents, 690
Phenylhydroxylamine, 907
Phenyllithium, in aryl halide ring closure, 502
  conversion to vinyllithium, 475
  reaction, with chlorocyclopentene, 280
    with dihalides, 770
    with episulfides, 769
    with quaternary ammonium salts, 761
Phenylmagnesium bromide, reaction, with aryl ketones, 605
    with unsaturated ketones, 604
  structure of, 150
Phenylmalononitrile, 647
1-Phenyl-4-mesityl-2,3-benzofuran, 632
3-(Phenylmethylamino)-4-phenyl-1-butene, 826
N-Phenyl-N-methylformamide, 418
Phenyl α-naphthoate, 558
2-Phenyl-1-nitrocyclohexene, 736
2-Phenyl-1-nitroethylene, 697
4-Phenyl-4-oxobutanoic acid, 415
5-Phenyl-2,4-pentadienoic acid, 641
3-Phenylpropanal, 911
3-Phenylpropanoamide, 911
2-Phenylpropanoic acid, 783
3-Phenylpropanoic acid, 804
1-Phenyl-2-propanol, 254
3-Phenyl-1-propanol, 593, 679
2-Phenylpropanoyl chloride, 414
1-Phenylpropene, 454, 566
3-Phenyl-2-propen-1-ol, 679

α-Phenylpropiophenone, 784
2-Phenyl-2-propyl carbanion, 144
1-Phenyl-2-propyl ethyl ether, 254
Phenyl radicals, 528
Phenylsodium, 766
2-Phenyl-1-tolylethane, 410
Phenyltrienes, 836
Phenyl trifluoroacetate, 677
Phenyltrihalomethylmercury, 644
6-Phenyl-5-triphenylacetoxy-1,3-cyclohexadiene, 605
Phosgene, in chlorinations, 533
  reaction, with acid salts, 325
    with alcohols, 319, 320
    with amines, 335
    with aromatic rings, 420
    with formamides, 778
  structure of, 914
Phosphine oxides, 705, 718
Phosphines, formation of, 332, 351, 474
  in isocyanate cycloadditions, 718
  reaction, with alkyl halides, 332, 702
    with epoxides, 334, 708
    with halocarbenes, 703, 704
    with olefins, 703
  reduction of amine oxides, nitrile oxides, and azoxy compounds, 901
Phosphinic acid salts, 148
Phosphonates, carbanions from, 148
  conversion to ylides, 705
  formation of, 705
Phosphonitriles, 38
Phosphoranes, formation of, 369, 702
  reaction, with acid derivatives, 369
    with aldehydes and ketones, 702–709
    with epoxides, 356
    with esters, 369, 703
    with olefins, 649
    in Wittig reaction, 702–709
Phosphoric acid, 327, 753
Phosphoric acid anhydrides, 327
Phosphorus, Walden inversion at, 254
Phosphorus-hydrogen iodide, reduction, of azlactones, 700, 902
    of hydantoins, 700
    of phenols, 505
Phosphorus oxychloride, in amide synthesis, 338
  in Bischler-Napieralski reaction, 422
  in formylations, 417, 463
  reaction, with alcohols, 326, 343
    with amides, 778
    with aryl halides, 504
Phosphorus pentabromide, 343, 677
Phosphorus pentachloride, in halogenations, 533
  reaction, with alcohols, 343
    with aldehydes and ketones, 677
    with amides, 684, 778, 849
Phosphorus pentachloride, reaction, with aromatic compounds, 504
    with esters, 347
    with malic acid, 253
    with oximes, 777, 821
    with sulfonic acids, 374
Phosphorus pentoxide, in acid cyclizations, 587
  in dehydration reactions, 325, 754, 755
  reaction, with acetals, 756
    with amides, 777, 778
    with ethers, 756
Phosphorus tribromide, 343, 460
Phosphorus trichloride, reaction, with alcohols, 343
    with sulfonic acids, 374
  reduction of amine oxides and azoxy compounds, 901
Phosphorus ylides (*see* Phosphoranes)
Photochemical cycloadditions, 634, 641
Photochemical rearrangements, 790*n*., 839, 841
Photochemistry, definition of, 175
Photolysis, definition of, 174
Photooxidation of dienes, 621
Photosensitizers, 622
Phthalaldehyde, 708
Phthalamic acid, 277
Phthalic acid, 277, 436
Phthalic anhydride, in alcohol dehydration, 745, 755
  formation of, 875
  in Perkin reaction, 699
Phthalidylideneacetic acid, 699
Phthalimide, 817
Pi bonds (*see* Orbitals, π)
Pi complexes, 66–69
  of alkenes with protons, 566
  in aromatic electrophilic substitution, 380–382, 395
  in aromatic rearrangements, 427
  in benzidene rearrangement, 829, 830
  stabilities of, 380–382
Picrates, 67
Picric acid, 224
Picric acid complexes, 67
Picryl chloride, 502, 507
Picryl iodide, 36
Pi-donors in complexes, 66, 68, 69
Pimelic acid, 871
Pinacolone, 798, 799
Pinacol rearrangement, 798
  migratory aptitudes in, 787
Pinacols (*see* 1,2-Diols)
Pinane, 922
Pinanes, 795*n*.
Pinner synthesis, 664
Pi orbitals (*see* Orbitals, π)
Piperidine as nucleophile, 271, 489, 490, 496, 502

Piperidines, formation of, 849
Pi-pi-star transitions, 171
Pi-star orbitals, 13
Pitzer strain, 120, 454
Pivalic acid, 913
pK values of acids, 19, 20, 219–221
Plain curves, 110
Plane of symmetry, 73, 76–78, 80, 98, 107, 108
Plane-polarized light (*see* Polarized light)
Platinum, as catalyst, in Arndt-Eistert reaction, 809
    for aromatizations, 860
    in hydrogenation, 680
    in reduction of anhydrides, 896
  reaction with hydrogen, 596
Platinum oxide, 592, 663
^{31}P nmr, 189
Poisoning of catalysts, 351
Polar reaction mechanisms, 199
Polarizability of dissymmetric molecules, 86
Polarized light, orientation of molecules in, 86
  rotation of plane of, 71, 83
    cause of, 86
    circular dichroism, 116
    in determining absolute configuration, 85
    factors affecting rotation, 72
    optical rotatory dispersion, 110
  (*See also* Circularly polarized light)
Polycyclic compounds, naming of, 925–928, 930
Polyhalo alkanes addition to olefins, 615
Polymerization, 142, 157, 570
Polyphosphoric acid, 414, 821
Polyurethans, 663
p orbitals, 5–8, 10
Potassium, 476, 798
Potassium amide, 143, 492, 493, 507
Potassium in ammonia, 354, 597
Potassium *tert*-butoxide (*see tert*-Butoxide ion)
Potassium chloride, 195
Potassium phthalimide, 340
Prefixes, in names, 915, 916
  order of, 919
5α,17α-Pregnane, 89
Prelog's rule, 651
Prevost method, 617
Primary isotope effects, 213–215
Prins reaction (addition of aldehydes to alkenes), 711
Prins reaction (formation of polyhalides), 615
Prismanes, 118, 119, 642
Product criterion for mechanisms, 205
Product spread, 270
Propadienediylidene, 161, 646
Propagation steps, 157, 522
Propane, bond energies of, 25
  dipole moment of, 19
  formation of, 117, 579
  reaction, with carbene, 164, 468
Propane, reaction, with ethylene, 601
1-Propanol, 786
2-Propanol, formation of, 215
  oxidation of, 864
  in reduction of aldehydes and ketones, 680
Propargyl cations, 128
Propargylene, 162
Propargyl vinyl ethers, rearrangement of, 833
Propene, bond angles of, 14*n.*
  formation of, 117, 468, 801
  reactivity of, 573
Propionic acid, 528
Propiophenone, 146, 911
Propylamine, 786
Propylbenzenes, 353, 408, 433
Propylcarbene, 466
Propyl cation, 268, 786
Propylferrocene, 434
Propyl halides reaction with benzene, 408
Propyne, 570
Propynylphenol, 455
Protic solvents, 224
  effect on ambident nucleophiles, 300
  in electrophilic substitutions, 447, 448
  nucleophilicity in, 288, 295
Protonated cyclopropanes, 267, 786
Protonated leaving groups, 290
Proton magnetic resonance [*see* Nuclear magnetic resonance (nmr)]
Prototropic rearrangements, 781
Pschorr ring closure, 551
Pseudoasymmetric carbons, 88
Pseudo-first-order reactions, 211, 252
Pseudorotation in five-membered rings, 109
Psi function, 3–6, 8, 28
Puckered rings, 105, 109
Pyran, 38
Pyrans, acylation of, 414
Pyrazoles, 674
Pyrazolones, 674, 893
Pyridine, basicity of, 41
  canonical forms, 38
  in dehydration reactions, 754
  in ester formation, 319–320
  orientation in, 390
  reaction with benzylic halides, 57, 883
Pyridine-N-oxide, 387
Pyridines, acylation of, 414
  alkylation of, 408, 509
  amination of, 510
  arylation of, 509
  formation of, 647, 667
  oxidation of, 886
Pyridinium cyclopentadienylide, 42
4-Pyridone, 61
Pyrolytic eliminations, 747–753
Pyrrole, aromaticity of, 40
  basicity of, 41

Pyrrole, in Diels-Alder reaction, 628
  orientation in, 390
Pyrroles, acylation of, 414
  formation of, 590
  formylation of, 419
  reaction with nitriles, 425
  ring expansion of, 647
Pyrrolidines, 332, 849
Pyrylium ions, 38, 709

Quadricyclene, 118
Quadrupolar nuclei, 195
Quadrupole coupling constants, 195
Quantum yield, 522
Quasi-Favorskii rearrangement, 808
Quasi-racemates method, 85
Quaternary ammonium hydroxides, cleavage of, 758
Quaternary ammonium salts, cleavage of, 761
  conversion to nitrogen ylides, 470
  formation of, 331
  optical activity of, 75
  rearrangement of, 516, 825
  reduction of, 351
Quaternary aziridium salts, 723
Quaternary hydrazonium salts, 776
Quaternary phosphonium salts, formation of, 332, 370, 702
  reduction of, 351
  in Wittig reaction, 702, 704, 705
Quinhydrones, 67
Quinoline, in decarboxylation, 435
  methylation of, 509
  reaction with acyl halides and cyanide ion, 352
Quinolines, acylation of, 414
  alkylation of, 408
  formation of, 423, 647, 667
Quinoline-sulfur, 351
Quinolinium salts, 690
Quinolizidine, 861
Quinone imines, 657
Quinones, addition reactions of, 568
  alkylation of, 553
  in aromatization, 861
  arylation of, 550, 552
  in complex formation, 67
  as dienophiles, 626
  epoxidation of, 620
  formation of, 414, 426, 657, 852, 865, 882 (*see also* 983)
  Michael addition, 604
  reaction, with diazomethane, 721
    with hydrazoic acid, 820
    with organometallic compounds, 685
    with sulfur tetrafluoride, 677
  reduction of, 679, 894
Quinuclidine, 486

Racemic acid, 93
Racemic compounds, 85
Racemic mixtures, creation of, 81
  properties of, 72, 85
  resolution of, 92
Racemization, of biphenyls, 78
  of carbonyl compounds, 458
  in electrophilic substitution reactions, 446–448
  in nucleophilic substitution reactions, 257
  in rearrangements, 784, 785
Radicals, in naming, 913, 915–920
  order of prefixes, 919
  (*See also* Free radicals)
Radicofunctional names, 920
Raman spectra, 181, 398
Raney nickel, in desulfurization, 439, 556
  in reduction, of aromatic ethers, 438
    of aryl halides, 440
    of multiple bonds, 592
    of nitriles, 684
    of nitro compounds, 908
    of thioamides, 895
  in removal of sulfo groups, 439
Rate constants, 208, 213
  correlated, by Hammett equation, 239
    by Taft equation, 242
Rate-determining step of reactions, 209
Rate laws, 208–212
Rates, 208–216
Reacting-bond rule, 236
Reactions, classification of, 200–202, 247–250
Reactivity, effects of structure on, 231–245
  quantitative treatments, 238–245
"Reagents for Organic Synthesis," 951
Rearrangements, 201, 202, 781–852
  acyl, 725, 726
  of alkylbenzenes, 433, 436
  allylic, 270–274, 449, 453, 586
    in acyloxylation, 545
    in Claisen rearrangement, 830, 831
    electrophilic, 459, 463
    free-radical, 527, 535
  of aromatic carboxylic acids, 436
  aryl, 427–432, 433–440, 514–520
    inter- versus intramolecular, 427–428
  of aryl halides, 439, 440
  of N-benzoylnorephedrine, 235
  of boranes, 456
  of carbanions, 152, 798
  of carbenes, 165
  of carbonium ions, 126, 139, 141, 782, 785
  of 1,3-diketones, 893
  of 2-formylcycloalkanones, 871
  in Friedel-Crafts alkylation, 408, 412
  in hydration of alkenes, 586
  of hydroperoxyboranes, 889
  of nickel carbonyls, 609

Rearrangements, in nitration of paraffins, 548
  nitrogen to oxygen, 780
  of oximes, 690, 784, 821
  in pyrolysis of alkyl chlorides, 750
  of radicals, 157, 790
Reduced mass, 214
Reductions, 853–857, 859, 860, 890–911
  of aldols, 701
  of alkyl halides, 348, 580
  of aryl ketones, 409
  of aryl substrates, 439, 505
  of azlactones, 700, 902
  definition of, 853
  of diazo ketones, 346
  of hydantoins, 700
  of keto epoxides, 345
  of keto sulfoxides, 369
  of ozonides, 871
  of phosphoranes, 370
  of radicals, 157
  selectivity, 890–892
  as side reaction in Grignard addition, 685, 687, 689, 690
  tables of reduction reactions, 859, 860
Reductive alkylation, of alcohols, 663
  of ammonia or amines, 668
Reductive cleavages, 902
Reductive coupling, 607, 903–908
Reed reaction, 546
Referativnyi Zhurnal, Khimiya, 941
Reformatsky reaction, 687
Refraction of light, 86
Reilly-Hickinbottom rearrangement, 432
Reimer-Tiemann reaction, 419
Reissert compounds, 352, 353
Replacement names, 920
Replicate names, 922
Reserpine, 423
Resolution, definition of, 72
  methods of, 91, 92
Resonance, 28–37
  in carbonium ions, 126–129
  effect on electronic spectra, 171–172
  nonclassical carbonium ions, 130–140
  rules of, 34
  steric hindrance to, 36
Resonance effects, 35
  and acid and base strength, 228
  in aromatic substitution, 384–387
  on reactivity, 231, 243
Resonance energy, 29–33, 39, 41, 52
Resonance integral, 29
Resorcinol, 915
Restricted rotation, and geometrical isomerism, 94
  and optical activity, 76–79
Retention of configuration, in carbanion reactions, 147, 148
Retention of configuration, in electrophilic substitutions, 443–449
  in free-radical substitutions, 525
  in nucleophilic substitutions, 253, 259, 263–264, 268
  in rearrangements, 783, 784, 786
Retropinacol rearrangement, 796
Reverse hyperconjugation, 58
Review articles, 945
Rhodanine, 700
Rhodium catalysts, in hydroformylation, 610*n.*
  in hydrogenation of multiple bonds, 592
Rhodium chloride, 603
Rho-values, 239–242, 245, 394–395
Rho-*I* values, 242
Richter system, 943*n.*
Ricinoleic acid, 779
Ring-chain tautomerism, 62
Ring-contraction reactions, 799–801
  of 2-formylcycloalkanones, 871
  of α-halo ketones, 804
Ring current, 185, 194
  of annulenes, 52–55
  in definition of aromaticity, 38
Ring-expansion reactions, 799–801
  of aromatic rings, 647
  of cyclic azides, 818
  of cyclic ketones, 811, 820, 823
  of cyclopropylmethyl systems, 139
  of divinylcycloalkanes, 835
  of vinylcycloalkanes, 837
"Ring Index," 924*n.*, 945
Ring systems, index of, 940
Ritter reaction, 715
"Rodd's Chemistry of Carbon Compounds," 949
Rosanoff convention, 82
Rosenmund reduction, 351
Rosenmund-von Braun reaction, 506
Rotation of plane of polarized light, 71, 83
  cause of, 86
  factors affecting, 72
Rotational barriers, 102, 196
  determination of, 182
Rotational levels, 169, 170
Rotational transitions, 175, 182
RS system of absolute configuration, 84, 87, 88
Ruthenium, 592, 680
Ruzicka cyclization, 371

Sacrificial hyperconjugation, 58
Salt effect in S_N1 reactions, 257, 295
Sandmeyer reaction (halides), 554
Sandmeyer reaction (nitriles), 555
Sandwich compounds (*see* Ferrocenes, Metallocenes)
Sandwich diradicals, 556

Saponification, 309
Saytzeff elimination (*see* Zaitsev elimination)
Saytzeff's rule (*see* Zaitsev's rule)
s character measured by nmr, 193
Schiemann reaction, 513
Schiff bases (*see* Imines)
Schlenk equilibrium, 149, 150
Schmidt reaction, 783, 819
Scholl reaction, 412
Schotten-Baumann procedure, 319, 335
Schrödinger equation, 3, 7, 8
S configuration, 84, 87, 88
$\mathrm{S_E}C$ mechanism, 452
Secondary isotope effects, 215
Second-order reactions, 208, 212
Seeding as method of resolution, 94
$\mathrm{S_E}$i mechanism, 443–446, 451
$\mathrm{S_E}$i′ mechanism, 450
Selection rules in Raman spectra, 182
Selectivity, of carbenes, 164
  of free-radical abstractions, 526
  in reductions, 890–892
Selectivity relationship, 394
Selenides, formation of, 329
Selenium, 473, 861
Selenium dioxide, 861, 880
Semibenzilic mechanism, 808
Semicarbazide, formation of, 657, 897
  reaction with aldehydes and ketones, 237, 674
Semicarbazones, formation of, 237, 674
  hydrolysis of, 657
Semidines, 828
Semipinacol rearrangement, 799
Semiquinones, 158
$\mathrm{S_E}1$ mechanism, 446–449
  in aromatic substitution, 396, 435, 436
  effects of structure and solvent on, 451
Sequence rules for RS system, 84
$\mathrm{S_E}2$ mechanism, 442–446, 451
$\mathrm{S_E}2'$ mechanism, 450
p-Sexiphenyl, 412
$\mathrm{S_F}2$ mechanism, 443
Shielding in nmr, 183–185, 194
$\mathrm{S_H}1$ and $\mathrm{S_H}2$ steps, 523
Sideband technique, 185
Sigma bonds (*see* Orbitals, σ)
Sigma complexes, in aromatic substitution, 376, 379, 380
  stabilities of, 380–385
Sigma-complex mechanism, 376–382
Sigma-minus values in Hammett equation, 240, 241, 498
Sigma orbitals (*see* Orbitals, σ)
Sigma-plus values, in aromatic substitution, 394–395
  in Hammett equation, 240, 241
Sigma-sigma-star transitions, 171
Sigma-star orbitals, 8
Sigma-star values, 240*n*., 242*n*.
Sigma-substitution mechanism, 401
Sigma values in Hammett and Taft equations, 239–243
Sigma-*I* values, 242, 243
Sigma-*R* values, 243
Silanes, 474
Silenes, 162
Silicic esters, 339
Silicon, Walden inversion at, 254
Silver, 354, 863
Silver acetate, 618
Silver benzoate, 618
Silver carboxylates, 559
Silver fluoride, 342
Silver ions, 300, 653
Silver nitrate, reaction, with alkyl halides, 327
    with alkyllead compounds, 474
    with boranes, 556
    with dibromobicyclohexane, 800
Silver oxide, in Arndt-Eistert synthesis, 809
  in oxidation of aldehydes, 539
  reaction, with malic acid, 253
    with quaternary ammonium salts, 758
Simmons-Smith procedure, 648
Simonini reaction, 559
Singlet states, 160, 161
Six-center reactions, 202
Skatole, 191
Skew conformation, 103
Skew boat conformation, 105
Skraup synthesis, 423
Small-angle strain, 117–119, 290
Smiles rearrangement, 519
$\mathrm{S_N}$i mechanism, 268, 333, 344, 504
$\mathrm{S_N}$i′ mechanism, 272, 517
$\mathrm{S_N}1$cA mechanism, 290, 310
$\mathrm{S_N}1$cB mechanism, 293, 304, 326, 334, 644
$\mathrm{S_N}1$ mechanism, 256–260
  at aliphatic trigonal carbon, 274, 278
  in aryl systems, 491
  effect of leaving group on, 290
  effect of medium on, 293
  effect of nucleophile on, 287
  effect of substrate structure on, 281–287
  versus E1, 734, 744–747
  in hydrolysis of esters, 310
  mixed $\mathrm{S_N}1$ and $\mathrm{S_N}2$ mechanisms, 261–263
  in rearrangement reactions, 785
  in reductions of alkyl halides, 348
  steric effects on, 233
  with sulfonyl halides, 372
$\mathrm{S_N}1'$ mechanism, 270–274
$\mathrm{S_N}2$cA mechanism, 290, 310
$\mathrm{S_N}2$ mechanism, 251–255
  at allylic carbon, 271
  in aryl systems, 494

- S_N2 mechanism, effect of leaving group on, 290
  - effect of medium on, 295
  - effect of nucleophile on, 287
  - effect of substrate structure on, 233, 281–287
  - evidence for, 252–255
  - versus E2 mechanism, 728, 738, 744–746
  - in Friedel-Crafts alkylation, 412
  - in hydrolysis of esters, 310
  - ion pairs in, 260
  - in metal hydride reductions, 348
  - mixed S_N1 and S_N2 mechanisms, 261
  - in rearrangement reactions, 785, 786
  - at sulfur atom, 372
  - at trigonal carbon, 274, 280
- S_N2' mechanism, 271, 273
- Sodium, in acyloin condensation, 904, 905
  - in alkylation of olefins, 602
  - in ammonia, in desulfurizations, 557*n*.
    - in reduction, of aromatic rings, 597
      - of aryl ethers, 505
      - of oximes, 899
      - of phosphites, 505
      - of quaternary salts, 351
  - in ethanol, reduction of aldehydes and ketones, 682
    - (*See also* Ethoxide ions)
  - in ethylene glycol, 763
  - reaction, with active hydrogen compounds, 357
    - with alcohols and copper bronze, 888
    - with alkenes, 607
      - and aldehydes or ketones, 713
    - with alkyl halides, 354
    - with dihalocyclopropanes, 644
    - with diketones, 847
    - with β-halo ethers, 771
  - rearrangement of alkyl halides, 798
  - reduction, of aldehydes and ketones, 682, 903
    - of imines, 903, 904
- Sodium aluminum hydride, 352, 684
- Sodium amalgam, 350, 351, 903
- Sodium amide, in alkylation of carboxylic acids, 602
  - reaction, with active hydrogen compounds, 357, 368
    - with alkyl halides, 765
    - with aryl halides, 502
    - with ethers, 755, 827
    - with ketones, 483
    - with pyridines, 510
    - with quaternary salts, 516, 825, 826
- Sodium ammonium tartrate, 93
- Sodium arsenite, 348, 907
- Sodium borohydride, reduction, of acyl halides, 897
  - of aldehydes and ketones, 678, 679, 681
  - of alkyl halides, 348
  - of $C{=}N$ compounds, 682
  - of diazonium salts, 514
  - of double bonds, 593
  - of esters, 896
  - of nitriles, 683
  - of nitro compounds, 505
  - of ozonides, 871
  - of tosylhydrazones, 894
  - reaction, with mercury compounds, 471, 582
    - with nitro compounds, 897
  - in reductive alkylation, 669
  - selectivity of, 890, 893
- Sodium fluorenide, 146
- Sodium fluoride, 343
- Sodium hydride, 368
- Sodium hydrosulfite, 902
- Sodium hypophosphate, 684
- Sodium iodide in acetone, reagent for alkyl halides, 342
- Sodium β-naphthoxide, 300
- Sodium perborate, 889
- Sodium peroxide, 326
- Sodium rubidium tartrate, 83
- Sodium stannite, 514
- Solvation, of carbanions, 447, 448
  - effect on acidity, 229
  - of nucleophiles, 288
- Solvation rule, 237
- Solvent, effect of, on electrophilic substitution, 447, 451
  - on elimination reactions, 745, 476
  - on free-radical substitutions, 531
  - on nucleophilic substitutions, 293
  - on stereospecificity, 565
- Solvent acidity, measurements of, 224
- Solvent isotope effects, 216
- Solvolysis, definition of, 251
- Sommelet-Hauser rearrangement, 516
- Sommelet reaction, 883
- Sonn-Müller reduction, 684
- *s* orbitals, 5–8
- Sorensen method, 358
- Special salt effects in S_N1 reactions, 259, 296
- Specific acid and base catalysis, 226, 227
- Specific rotation, 73
- Spectrophotometers, 169
- Spherical coordinates, 3
- Spin, electron, 7, 153, 196
- Spin number of nuclei, 182, 188
- Spin-spin coupling, 186–191, 196
- Spiro compounds, formation of, 360, 644, 645
  - naming of, 928
  - optical activity of, 79
- Spiropentanes, formation of, 644, 645
- Splitting of nmr and epr peaks, 186–191, 196
- *sp* orbitals (*see* Orbitals, *sp*)
- sp^2 orbitals (*see* Orbitals, sp^2)
- sp^3 orbitals (*see* Orbitals, sp^3)

- Squaric acid and dianion, 55
- Staggered conformations, 102
- Stannic chloride, 407, 712
- Stannous chloride, reduction, of alkyl halides, 348
    - of nitriles, 684
    - of nitro compounds, 901
- Statistical effects on acid and base strength, 228
- Steady-state assumption, 210
- Stearaldehyde, 352
- Stephen reduction, 684
- Stereochemistry, 71–124
  - mechanistic information from, 207
- Stereoisomerism, 71–100
- Stereoselective synthesis, definition of, 101
- Stereoselectivity, in addition, to double bonds, 566, 569–571, 578
    - to triple bonds, 564–565, 569–571
  - in elimination reactions, 730–732
- Stereospecificity, in addition, of carbenes, 160, 161, 645, 646
    - to double bonds, 563–565, 569, 591
  - in Diels-Alder reaction, 629, 631
  - in elimination reactions, 728–729, 733, 734, 742, 748
  - of hydrogenation of alkenes, 594
  - in rearrangement of cycloalkenes, 839–841
  - in solvolysis of 3-phenyl-2-butyl tosylate, 132
  - (*See also* Inversion of configuration; Retention of configuration)
- Stereospecific synthesis, definition of, 101
- Sterically crowded molecules, 122
- Steric effects, and acid and base strength, 228
  - quantitative correlation of, 244
  - on reactivity, 233
- Steric hindrance, 124
  - in nucleophilic substitution, 233
  - to resonance, 36, 144
- Steroids, designation of asymmetric positions, 88
  - rearrangement of, 795*n*., 797
- Stevens rearrangement, 825
- Stilbene, electronic spectrum of, 174
  - formation of, 748, 879, 887–888
  - isomerization of, 175
  - reaction with bromine, 565
- Stiles-Sisti reaction, 438
- Stobbe condensation, 696
- Stork enamine reaction, 464, 482
- Strain, 116–124
  - in small rings, 117, 290
- Strecker synthesis, 710
- Stretching vibrations, 178
- Strychnine, 481
  - structure of, 167, 168
  - use for resolution, 92
- Styrene, coupling of, 608
  - 2 + 2 cycloadditions of, 636, 639
- Styrene, in Diels-Alder reaction, 628
  - formation of, 738, 760
  - reaction with toluene, 602
- Styrene oxide, 350
- Substitutive names, 915
- Subtractive names, 921
- Successive-labeling-isotope effects, 271
- Succindialdehyde, 671
- Succinic acid derivatives, bisdecarboxylation of, 879
- Succinic anhydride, 415
- Succinimidyl radicals, 537
- Suffixes in names, 915, 916, 929
- Sulfamoyl chloride, 333
- Sulfenyl chlorides, addition to alkenes, 613
  - formation of, 547
- Sulfhydride ions, reaction, with acid derivatives, 329
    - with alkyl halides, 328
    - with aryl halides, 500
    - with diazonium salts, 512
  - reduction of nitro compounds, 897
- Sulfide ions, reaction, with alkyl halides, 329
    - with aryl halides, 501
    - with diazonium salts, 512
  - reduction of sulfonyl chlorides, 374
- Sulfides, acetylenic, 583
  - acyloxylation of, 545
  - in alkylation of aromatic rings, 407
  - cleavage of, 764
  - conversion to sulfonium salts, 329
  - desulfurization of, 556
  - formation of, 328, 402, 473, 500, 512, 587, 588, 613, 764, 896, 901, 902 (*see also* 983)
  - oxidation of, 887
  - reaction with diazonium ions, 512
- Sulfinic acid esters, conversion to alcohols, 305
  - optical activity of, 76
- Sulfinic acids, formation of, 374, 764
- Sulfinic acid salts, conversion to sulfones, 330, 501
- Sulfite ions, reaction, with alkyl halides, 330
    - with aryl halides, 501
    - with Bunte salts, 373
    - with osmic esters, 617
  - reduction, of diazonium salts, 899–900
    - of sulfonyl chlorides, 374
- Sulfonamides, addition to multiple bonds, 590
  - alkylation of, 340, 357
  - carbanions from, 148
  - conversion to sulfonates, 373
  - formation of, 340, 357, 374 (*see also* 983)
  - N-halogenation of, 487
  - hydrolysis of, 373
  - reduction of, 351
- Sulfonates (*see* Sulfonic acid esters, salts)
- Sulfonation, at aliphatic carbon, 462
  - of aromatic rings, 401

Sulfonation, of naphthalene, 383
Sulfones, addition to activated olefins, 604
  alkylation of, 357
  carbanions from, 148
  cleavage of, 764
  condensation with aldehydes and ketones, 679
  formation of, 330, 357, 375, 401–403, 501, 613, 887 (*see also* 984)
  optical activity of, 75
  oxidation of, 885
  reduction of, 901
Sulfonic acid esters, alkylation of, 357
  in alkylation of aromatic rings, 407
  condensation with aldehydes and ketones, 697
  conversion, to alcohols, 305
    to amines, 502
    to halides, 343
    to hydroperoxides, 326
    to peroxides, 326
    to sulfones, 375
  ethanolysis rates, 284
  formation of, 326, 327, 357, 373, 427, 584 (*see also* 984)
  hydrolysis of, 372, 373
  oxidation to aldehydes, 882
  pyrolysis of, 758
  reaction, with acetylides, 361
    with acid salts, 324
    with active hydrogen compounds, 360
    with amide salts, 340
    with ammonia and amines, 331
    with cyanide ion, 361
    with Grignard reagents, 355
    with sulfur nucleophiles, 328, 330
  reduction of, 505
  S—O versus C—O cleavage of, 373
Sulfonic acids, conversion to sulfonyl halides, 374
  desulfonation of, 439
  formation of, 330, 373, 401, 436, 439, 462, 501, 589, 885 (*see also* 984)
  reaction, with alkenes, 584
    with ethers, 327
Sulfonic acid salts, alkali fusion of, 500, 502
  conversion, to amines, 502
    to nitriles, 506
Sulfonium hydroxides, cleavage of, 764
Sulfonium salts, cleavage of, 764
  formation of, 329
  optical activity of, 76
Sulfonylation of aromatic rings, 403
Sulfonyl halides, addition to alkenes, 613
  conversion, to sulfonamides, 373
    to sulfones, 375
    to sulfonic acid esters, 373
  formation of, 374, 402, 546
Sulfonyl halides, hydrolysis of, 373
  reaction, with aromatic rings, 403
    with free radicals, 528
    with nucleophiles, 372–375
  reduction of, 374, 900
Sulfonylhydrazides, 374
Sulfoxides, carbanions from, 148
  cleavage of, 764
  condensation with aldehydes and ketones, 697
  desulfurization of, 556
  formation of, 369, 403, 887
  optical activity of, 76
  oxidation of, 885, 887
  reduction of, 901
Sulfur, in aromatization, 860
  reaction, with aromatic rings, 403
    with diazo compounds, 722
    with Grignard reagents, 473
    with ketones and amines, 910, 911
  reduction, of amine oxides and azo compounds, 901
    of sulfoxides and sulfones, 901
  Walden inversion at, 254
Sulfur chloride, 402–404
  reaction with alkanes, 547
Sulfur dioxide, in clathrate compounds, 70
  reaction with alkanes and chlorine, 546
Sulfuric acid, in alcohol dehydration, 317, 753
  conversion to mixed anhydrides, 327
  in Friedel-Crafts reaction, 407, 408, 414
  in hydroxyalkylation, 421
  in Jacobsen reaction, 436
  in lactone formation, 587
  reaction, with ethers, 306, 307
    with iodobenzenes, 440
    with nitro compounds, 659
    with olefins, 581, 584
  in Skraup synthesis, 423
  in sulfonation of aromatic rings, 401
Sulfurization of aromatic rings, 402
Sulfur tetrafluoride, reaction, with alcohols, 344
    with alkenes, 611
    with carbonyl compounds, 677
Sulfur trioxide, reaction, with alcohols, 326
    with aldehydes, ketones, and acids, 462
    with aromatic rings, 401, 402
Sulfuryl chloride, reaction, with aldehydes, 538
    with alkanes, 533
    with carbonyl compounds, 459
Sulfur ylides (*see* Ylides, sulfur)
Superimposability of molecules on mirror images, 71, 73–82, 98
Sydnones, 55
Symmetry, of molecules, 73, 86
  orbital, conservation of, 633–636, 639, 641, 837*n.*, 839–841
Syn-anti isomerism, 95

Syn-periplanar conformation, 731, 759
"Synthetic Organic Chemistry," 951

Taft equation, 241, 243
Tartaric acid, 83, 93
  optical isomers of, 87
  properties of, 72
Tautomerism, 59–62
  measurement of, 174, 192
Tautomerization, 446, 457
Tau value, definition of, 186
Tellurium, 473
Terephthalamic acid, 277
Termination steps, 156, 521
Terpenes, rearrangement of, 795, 796
Terphenyls, 434
Terphthalic acid, 436
α-Terpinene, 622
Tetrabromo compounds, formation of, 612
2,4,4,6-Tetrabromo-2,5-cyclohexadienone, 802
Tetrabutylammonium halides, 288
Tetra-*tert*-butylbenzenes, 123
Tetra-*tert*-butylmethane, 123
1,1,3,3-Tetracarbethoxypropane, 698
1,2,5,6-Tetracarbomethoxy-1,5-cyclooctadiene, 838
1,2,5,6-Tetracarbomethoxytricyclo[4.2.0.$0^{2,4}$]-octane, 838
Tetracyanoethylene, in complex formation, 67
  conversion to cyclopropanes, 644
  as dienophile, 633
  reactivity of, 574
7,7,8,8-Tetracyanoquinodimethan, ion-radical from, 158
Tetracyclo[2.2.1.$0^{2,6}$.$0^{3,5}$]heptane, 118
Tetracyclo[2.2.0.$0^{2,6}$.$0^{3,5}$]hexane, 118
Tetracyclo[4.3.0.$0^{2,9}$.$0^{3,7}$]nonane, 628
Tetraethylferrocene, 435
Tetraethyllead, 476
Tetraethyl monothiopyrophosphate, 189
1,1,4,4-Tetrafluorocyclohexadienes, 677
Tetrafluoroethylene, 574
  conversion to cyclobutanes, 637, 640
  fluorination of, 611
  reaction with oximes, 586
2,2,3,3-Tetrafluoro-1-ethynylcyclobutane, 640
3,3,4,4-Tetrafluoro-1-vinylcyclobutene, 640
Tetrahedral intermediates, isolation of, 277, 278, 489
Tetrahedral mechanism, 274–278, 652
  of acyl cleavages, 481
  in aldehyde oxidation, 541
  in amide hydrolysis, 314
  in Claisen condensation, 367
  effect, of nucleophile on, 289
    of substrate structure, 281, 286
  evidence for, 275–277
Tetrahedral mechanism, in hydrolysis of acid derivatives, 308–310
  in ketonic decarboxylation, 371
  at vinyl carbon, 283
Tetrahydrocyperones, 113
Tetrahydrofuran, formation of, 597
  reduction of, 350
  as solvent for Grignard reagents, 150
Tetrahydrofurans, formation of, 542, 597
Tetrahydrophenanthrene, 628
2,4,5,6-Tetraiodo-1,3-dimethylbenzene, 439
Tetrakis[24]dehydroannulene, 54
Tetralin, 409
Tetralone, 415
Tetramethylammonium hydroxide, 759
Tetramethylammonium ion, 145
2,3,7,8-Tetramethyl-5-azoniaspiro[4.4]nonane tosylate, 74
Tetramethylbenzenesulfonic acid, 436
2,2,8,8-Tetramethyl-3,7-bis(*p*-chlorophenyl)-3,4,5,6-nonatetraene, 79
1,5,5,6-Tetramethylcyclohexene, 603
Tetramethylcyclopropanone, 806
2,2,4,5-Tetramethyl-3,5-dichlorohexane, 567
2,2,5,5-Tetramethyl-3,4-hexanedione, 905
2,2,5,5-Tetramethyl-3-hexene, 873, 874
Tetramethylphosphonium ion, 145
Tetramethylsilane, 185
1,1′,3,3′-Tetraphenyl-$\Delta^{2,2'}$-biimidazolidine, 159
Tetraphenylcyclobutenium dictation, 49
1,1,2,2-Tetraphenylethanol, 697
1,1,3,3-Tetraphenyl-2-propen-1-ol, 604
Tetrasulfides, formation of, 330
1,1′,3,3′-Tetra-*p*-tolyl-$\Delta^{2,2'}$-biimidazolidine, 159
Tetravinyltin, 475
Textbooks, 950
Thallium acetate, 618
Theilheimer's "Synthetic Methods of Organic Chemistry," 951
Theobromine, 914
Thermodynamically-controlled products, 204
Thermodynamic requirements for reaction, 202
2-Thienylcopper, 508
10-(2-Thienyl)decanoic acid, 557
9-(2-Thienyl)nonanoic acid, 557
Thiiranes (*see* Episulfides)
Thioacetals, formation of, 588, 665
Thioaldehydes, reaction with sulfur, 722
Thioamides, desulfurization of, 556
  formation of, 416, 691, 910
  reduction of, 895
Thioaroxyacetylenes, 279, 280
1-Thioaroxy-2-chloroethylenes, 279, 280
1-Thioaroxy-2,2-dichloroethanes, 280
Thiocarbamates, formation of, 661, 663
N,N′-Thiocarbonyldiimidazole, 768
Thiocyanate ion, reaction, with alkyl halides, 330, 342

Thiocyanate ion, reaction, with aryl halides, 501
    with Bunte salts, 329
    with diazonium salts, 512
Thiocyanates, in alkylation of aromatic rings, 407
  coupling of, 507
  formation of, 330, 501, 512
  hydrolysis of, 661
  reaction with aromatic rings, 425
Thioethers (*see* Sulfides)
Thiol acids, addition to multiple bonds, 588
  conversion to amides, 339
  coupling of, 889
  formation of, 329
Thiol esters, conversion to amides, 339
  formation of, 329, 425, 583, 588, 609, 691 (*see also* 985)
  hydrolysis of, 310
  oxidation of, 885
  reduction of, 896
Thiols (*see* Mercaptans)
Thiones, formation of, 665
  reaction with sulfur, 722
α-Thiono acids, 700
Thionocarbonates, 768
Thionyl bromide, 343
Thionyl chloride, reaction, with alcohols, 269, 326, 343
    with amides, 778
    with aromatic rings, 403
    with butenols, 272
    with carboxylic acids, 346
    with malic acid, 253
    with nitro compounds, 504
    with oximes, 776, 777
    with propargyl alcohols, 272
    with sulfonic acids, 374
Thionyl fluoride, 678
Thiophene, aromaticity of, 40
  in Diels-Alder reaction, 628, 632
  orientation in, 390
Thiophenes, acylation of, 414
  alkylation of, 408
  desulfurization of, 557
  formation of, 588
Thiophenols, 385
Thiophosgene, 335
Thiosulfate ions reaction with alkyl halides, 330
Thiourea, inclusion compounds of, 70
  reaction, with alkyl halides, 328
    with Bunte salts, 329
Thioureas, formation of, 673
Thorium oxide, 352, 370, 754
Thorpe reaction, 693, 709
Thorpe-Ziegler reaction, 709, 907
threo as prefix, 89
Tiffeneu-Demyanov ring expansion, 800
Tiglic acid, 449
Tin, reduction, of alcohols, 349
    of aryl halides, 440
    of nitro compounds, 897
    of quinones, 894
Tishchenko reaction, 910
Titanium tetrachloride, 815, 908
Title publications, 937
Tollen's reaction, 693, 701
Toluene, acylation of, 391, 409, 428
  alkylation of, 395, 409, 410
  amination of, 400
  bromination of, 395, 531
  chlorination of, 387
  dipole moment of, 19, 57
  formation of, 429, 647
  hyperconjugation in, 57
  mass spectrometry of, 43
  nitration of, 388, 395
  reaction, with carbenes, 647
    with styrene, 602
  substitution rates, 394, 395
p-Toluenesulfonic acid, 318
p-Toluenesulfonyl chloride, 778
p-Toluenesulfonylhydrazones, 763
Toluidines, 432
o-Toluophenone, 410
m-Toluyl isocyanate, 416
Tolyl benzyl ether, 429
p-Tolyl benzyl sulfone, 75
Tolyl butyl ether, 429
o-Tolylpropenes, 833
p-Tolyl sulfide, 24
Topochemistry, 641
Torsion angle, 102
Tosylates, definition of, 305
Tosylhydrazones, decomposition of, 763
  reduction of, 894
Transacetalation, 622
Trans addition to multiple bonds, 563–566, 569–571, 578, 579, 594, 617
Transamination, 333, 374, 503
Transannular interactions, 119–121
Transannular reactions, 121, 466, 612
Transannular rearrangements, 121, 789, 793, 847, 848
Trans conformation, 103
Trans cycloalkenes, 80, 96, 122
  formation of, 760, 762
Trans elimination, 728–731, 733, 761, 769
Transesterification, 322, 423
Transetherification, 318, 500
Transfer hydrogenation, 593
Trans isomers, 94–100
Transition state, definition of, 203
Treatises, 947–950
Triacylamines, 335
1,3,5-Triacylperhydro-1,3,5-triazines, 718
Trialkylacetyl cations, 129

Trialkylammonium peroxides, 886
Trialkylphosphines, 704, 706, 707
Triarylacetic acids, 315
Triazenes, in arylation reactions, 551
  formation of, 399, 431, 487
  rearrangement of, 431
Triazines, formation of, 720
Triazoles, 625
Triazolines, 623
Tribromobenzenes, 439
2,4,6-Tribromophenol, 802
Tri-*tert*-butylamine, 123
Tri-*tert*-butylbenzenes, 123
Tri-*tert*-butylcarbinol, 123, 686
Tributyltin hydrides, 351
1,2,3-Tri-*tert*-butyl-4,5,6-trifluorobenzene, 123, 642
Trichloroacetic acid, conversion to dichlorocarbene, 163, 644
Trichloroacetonitrile, 425, 673
1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane (*see* DDT)
Trichloroethylene, 580, 736
3,5,6-Trichloro-2-hydroxy-1,4-cyclohexanedione, 278
Trichloromethanesulfonyl halides, 534
Trichloromethyl methyl sulfone, 644
1,1,1-Trichloro-2-methyl-2-propanol, 697, 814
3,3,3-Trichloropropene, 573, 792
1,2,2-Trichlorovinyldiethylamine, 344
Tricresyl phosphate, 504
Tricyanoethylene, 574
Tricyclo[2.2.0.$0^{2,6}$]hexane, 118
Tricyclo[1.1.1.$0^{2,4}$]pentane, 118
Tricyclopropylmethyl cation, 128
Trideuteriomethoxycyclohexane, 106
1,3,5-Trienes, rearrangement of, 835, 839–841
Triethylamine, 151, 723
Triethylferrocene, 435
Triethylphosphine, 907
Triethyl phosphite, in desulfurization, 557*n*.
  reaction, with disulfides, 902
    with epoxides and episulfides, 769
    with peroxides, 902
1,1,1-Trifluorides, formation of, 677
Trifluoroacetic acid, 304
Trifluoroacetic anhydride, 322, 336
Trifluoroacetonitrile, 709
2,2,2-Trifluoro-1,1-dichlorophenoxyethane, 677
Trifluoroiodomethane, 615
Trifluoromethane, 59
Trifluoroperacetic acid (*see* Peroxytrifluoroacetic acid)
3,3,3-Trifluoropropene, 576
α,α,α-Trifluorotoluene, 304
1,2,6-Trifluoro-3,4,5-tri-*tert*-butylbicyclo[2.2.0]hexadiene, 642
1,2,3-Trifluoro-3,4,5-tri-*tert*-butyltetracyclo[2.2.0.$0^{2,6}$.$0^{3,5}$]hexane, 118, 642
Trigonal hybridization, 11
1,1,1-Trihalides, in alkylation of aromatic rings, 406
  conversion, to acids, 303
    to ortho esters, 316
  decarboxylation of, 478, 479
  formation of, 478, 677
Trihalo ketones, 339
Triisopropylcarbinol, 480, 686
Triisopropylmethyl cation, 127
Triketones, formation of, 369
Trimethylacetophenone, 435
Trimethylacetylcarbene, 165
Trimethylamine, basicity of, 229
  bond angles of, 24
  formation of, 758, 760
Trimethylanilines, 432
1,2,3-Trimethylbenzene, 382, 392
Trimethylbenzenesulfonic acid, 437
2,4,6-Trimethylbenzoates, 312
1,10,10-Trimethyl-9-benzoxybicyclo[4.4.0]dec-1,3-diene, 884
1,10,10-Trimethyl-9-benzoxybicyclo[4.4.0]dec-1-en-3,4-dione, 884
2,4,6-Trimethylbenzoyl cation, 129
2,4,6-Trimethylbenzyltrimethylammonium ion, 518
2,3,3-Trimethyl-2-chlorobutane, 733
2,4,4-Trimethyl-2-chloropentane, 739
2,4,6-Trimethylethylbenzene, 379
2,4,6-Trimethyl-1-ethylcyclohexadienyl fluoborate, 379
2,4,4-Trimethyl-2-pentene, 599
2,4,4-Trimethylpentenes, formation of, 739
2,2,4-Trimethyl-3-pentylborane, 599
2,4,6-Trimethylphenol, 426
Trimethyl phosphite, 768
2,N,N-Trimethylpiperidinium hydroxide, 758
2,6,N-Trimethylpyridinium iodide, 124
Trimethylsilylbenzenes, 393
Trimethylsulfonium ion, 145
2,4,6-Trimethyl-1,3,5-trinitrocyclohexane, 606
1,3,5-Trinitrobenzene, 606
2,4,6-Trinitrobiphenyl, 507
Trinitrophenol, 877
Trinitrophenol-benzidine complex, 68
Trinitrotoluene, 577
Trioxanes, formation of, 717
2,4,6-Trioxohexahydro-1,3,5-triazines, 719
Tripentylboranes, 814
Triphenylacetophenone, 605, 679
Triphenylarsine, 704
Triphenylcarbinol, alkylation with, 361
  cleavage of salt of, 480
  reaction with aromatic rings, 411

2,2,2-Triphenyl-1-chloroethane, 798
Triphenyldibromophosphorane, 345
Triphenylene, 40
1,1,2-Triphenylethane, 798
2,2,2-Triphenylethyl radical, 792
Triphenylgermylbenzenes, 393
Triphenylmethane, cyclization of, 412
  formation of, 406, 679
  metalation of, 469
Triphenylmethyl carbanion, 144
Triphenylmethyl cation, 128, 129, 864
Triphenylmethyl chloride, conversion to cation, 128
  formation of, 406
  reaction, with aromatic rings, 411
    with methanol, 261
Triphenylmethyl esters, formation of, 323
Triphenylmethyl radical, 154, 156, 531, 551–552
Triphenylmethylsodium, reaction, with active hydrogen compounds, 357
    with alkyl halides, 354
    with esters, 364
Triphenylphosphine, reaction, with diazo ketones, 657
    with epoxides, 334, 708, 769
  reduction, of amine oxides and azoxy compounds, 901
    of aryl halides, 440
    of nitroso compounds, 907
    of sulfoxides, 901
  in Wittig reaction, 702, 704
Triphenylphosphonium cyclopentadienylide, 704
Triphenylphosphonium β-ionylideneethylide, 708
Triphenylphosphonium methylide, 704
3,3,3-Triphenylpropanal, 792
Triphenyltin hydride, 440
Triple-bond compounds, addition reactions of, 562–726
  electronic structure of, 14
  formation of, 727, 728, 731, 736, 753, 760, 765, 771, 774
  in nmr, 184
Triple bonds in rings, 122
Triple-decker-sandwich compounds, 43
Triplet state, 156, 160, 161, 196
Tripropylbenzene, 433
Triptycene, 628
Trisdehydro[12]annulene, 54
Trisdehydro[18]annulene, 54, 549
Tris(3-ethylpentyl)boranes, 767
1,2,3-Tris(trimethylacetyl)cyclopropane, 165
1,3,5-Trithianes, 665
Tritiation of aromatic rings, 396
Tritium compounds, naming of, 931
Tritium isotope effects, 215
Tritricosaboranes, 815
Trivial names, 912, 923
Trivinylmethyl cations, 128
Tröger's base, 75
Tropic acid, 671
Tropine, 671
Tropinone, 671
Tropolones, 44
Tropone, 44
Tropylium bromide, 43
Tropylium ion, 43, 44, 129, 197, 411
Truxillic acids, 74, 641
Truxinic acids, 97, 641
Truxinic anhydride, 97
Twist conformation, 105, 106
Two-stage mechanism of aromatic nucleophilic substitution, 494

Ullman reaction (biaryl synthesis), 507
Ullman reaction (ether synthesis), 500
Ultraviolet spectra, 168
Umbrella effect, 75, 147, 446
10-Undecenoic acid, 779
Unsaturated acids, decarboxylation of, 477–479
  as dienophiles, 626
  formation of, 608, 649, 698, 704, 757, 812 (*also see* 985)
Unsaturated acyl halides, 626, 650
Unsaturated alcohols, cleavage of, 779
  as dienophiles, 626
  formation of, 698, 711–713, 800 (*see also* 985)
  rearrangement of, 456
Unsaturated aldehydes, addition of hydrogen cyanide, 610, 710
  addition reactions of, 568, 575
  in aldol condensation, 694
  alkylation of, 358
  cleavage of, 693
  condensation with anhydrides, 699
  conversion to quinolines, 423
  as dienophiles, 626
  epoxidation of, 620
  formation of, 272, 463, 616, 671, 692, 693, 697, 834, 842, 916 (*see also* 985)
  reaction, with ammonia, 667
    with Grignard reagents, 604, 685
Unsaturated amides, addition reactions of, 568
Unsaturated amines, as dienophiles, 626
  formation of, 603
Unsaturated diketones, formation of, 861
Unsaturated esters, addition reactions of, 568, 575
  condensation with aldehydes or ketones, 696
  as dienophiles, 626

- Unsaturated esters, epoxidation of, 619
  - formation of, 606, 649, 671, 688, 696, 697, 714, 807 (*see also* 985)
  - reaction with organolithium compounds, 605
- Unsaturated halides as dienophiles, 626
- Unsaturated ketones, addition of hydrogen cyanide, 610, 710
  - addition reactions of, 568, 575
  - alkylation of, 358, 360
  - cleavage of, 693
  - conversion to quinolines, 423
  - as dienophiles, 626
  - epoxidation of, 620
  - formation of, 272, 456, 463, 586, 606, 616, 650, 671, 692, 693, 697, 802, 833, 834, 842, 861, 916 (*see also* 985)
  - reaction with organometallic compounds, 604, 605, 685
  - rearrangement of, 832
  - reduction of, 679, 893
- Unsaturated nitriles, addition reactions of, 568, 575
  - as dienophiles, 626
  - formation of, 606, 610, 688, 697 (*see also* 986)
- Unsaturated nitro compounds, addition reactions of, 568, 575
  - as dienophiles, 626
  - formation of, 606, 614, 623, 697 (*see also* 986)
- Unsaturated quaternary ammonium hydroxides, pyrolysis of, 760
- Unsaturated sulfones, addition reactions of, 568
  - formation of, 697
- Unsaturated sulfonic esters, formation of, 606, 697 (*see also* 986)
- Unsaturated sulfoxy compounds, addition reactions of, 568
  - formation of, 697
- Unshared pair size, 12
- Urea, in carboxylation of aromatic rings, 420
  - inclusion compounds of, 69, 93
  - reaction with ethyl malonate, 340
- Ureas, formation of, 483, 658, 672, 817 (*see also* 986)
  - rearrangement of, 817
- Ureides, formation of, 340, 726, 817, 818
- Urethanes (*see* Carbamates)

- Valence bond method, 8, 9, 28
  - free valence in, 55
- Valence isomers, of benzene, 643
- Valence tautomerism, 842–844
- Vanadium (V), 857*n*., 865
- Vanadium pentoxide, 875
- Vanadium trichloride, 908
- van der Waals forces, 63, 69, 85
- Vapor phase chromatography, 93
- Veratrole, 923
- Vibration of molecules, 178
- Vibrational levels, 169, 170
- Vibrational transitions, 175, 179
- Vilsmeier (Vilsmeier-Haack) reaction, 417, 463, 616
- Vinylacetylene, bromination of, 575
  - formation of, 603
  - reaction with tetrafluoroethylene, 640
- 6-Vinylbicyclo[3.1.0]hex-2-ene, 835
- Vinyl carbanions, 145, 147
- Vinyl chloride, 33, 576
- Vinyl chlorides, 677, 762
- Vinylcycloalkanes, ring expansion of, 837
- Vinylcyclobutane, 837
- 1-Vinylcyclohexene, 627
- 4-Vinylcyclohexene, 626, 837
- Vinylcyclopropanes, formation of, 644
  - ring expansion of, 837
- Vinylene carbonate, 632
- Vinyl ethers (*see* Enol ethers)
- Vinyl halides, conversion, to alkynes, 765
    - to enol ethers, 812
    - to Grignard reagents, 475
  - formation of, 580, 612, 615, 616, 677, 762 (*see also* 986)
- Vinylidinecarbenes, 161
- Vinyllithium, 475, 812
- 1-Vinylnaphthalene, 628
- Vinylology, 358, 693, 696, 699
- Vinyl polymerization, 142, 157
- Vinyltriphenylphosphonium ions, 704
- Visible spectra, 168
- von Baeyer system, 924–926
- von Braun reaction, 346
- von Pechmann reaction, 423
- von Richter reaction, 205, 206, 514

- *w* (Bunnett value), 226, 312
- Wagner-Meerwein rearrangements, 794–798
- Walden inversion, 252–254
- Wallach reaction, 669
- Wallach rearrangement, 851
- Water, in Arndt-Eistert synthesis, 809
  - bond angles of, 10, 12, 24
  - clathrate compounds of, 70
  - dissociation energy of, 25
  - electronic spectrum of, 171
  - in Passerini reaction, 726
  - reaction, with aldehydes and alkynyl ethers, 714
    - with esters, 845, 846
    - with isonitriles, 725
    - with isopropyl bromide, 215
  - (*See also* Hydration; Hydrolysis)

Wave nature of electrons, 3
Whitmore 1,2-shift, 782, 798
Willgerodt reaction, 910
Williamson reaction, 316
Windshield wiper effect, 137
Wittig reaction, 693, 702–709
Wittig rearrangement, 827
Wohl-Ziegler bromination, 535
Wolff-Kishner reaction, 893–894
Wolff rearrangement, 165, 809
Woodward method, 618
Wurtz-Fittig reaction, 354
Wurtz reaction, 354

Xanthates, cleavage of, 750, 752, 757
  formation of, 664, 757
  reaction with diazonium ions, 512
Xanthyl cation, 773
Xenon tetrafluoride, 611
X-ray diffraction, 23, 97, 109, 167, 198
  to determine absolute configuration, 83
  of Grignard reagents, 150
m-Xylene, 382, 391
o-Xylene, 382, 388, 872
p-Xylene, 382
Xylenes, isomerization of, 433

Ylides, definition of, 42
  nitrogen, carbenes from, 163
    cleavage of, 747, 750, 759–761
    derived from cyclopentadiene, 42
    formation of, 470
    rearrangement of, 825
    stability of, 145
  phosphorus (*see* Phosphoranes)
  sulfur, cleavage of, 764
    reaction, with aldehydes and ketones, 721
      with alkynes, 361
      with esters, 369
      with imines, 723
      with nitro compounds, 509
      with olefins, 649
      with sulfur, 722
Ynamines, formation of, 766
Y-values of solvents, 296, 297

Zaitsev elimination, 730, 735, 746, 751, 752
  in borane elimination, 767
  in dehydration, 754
  in dehydrohalogenation, 765
  in double-bond shifts, 453
  in pyrolysis, of alkyllithiums, 767
    of quaternary ammonium hydroxides, 759
  in rearrangement reactions, 794, 796
Zaitsev's rule, 739–742
Zeisel method, 344
Zentralblatt, 941, 954
Zerewittenoff process, 471
Ziegler alkylation, 509
Zinc, reaction, with alkyl halides, 348, 354
    with dihalides, 770
    with α-halo acyl halides, 771
    with β-halo compounds, 771–772
    with ozonides, 871
  reduction, of anhydrides, 896
    of azo and azoxy compounds, 902
    of disulfides, 903
    of double bonds, 592
    of hydrazo compounds, 902
    of hydroxylamines, 898
    of nitro compounds, 897, 898, 908
    of nitroso compounds, 898
    of oximes, 899
    of phenols, 505
    of sulfonyl halides, 374, 900
  in reductive alkylation, 669
  in Reformatsky reaction, 687
Zinc amalgam, 891–894
Zinc chloride, in acid cyclizations, 587
  in acylation of aldehydes and ketones, 716
  in alcohol dehydration, 754
  in alkyl chloride formation, 343
  in anhydride formation, 324
  in carbamate formation, 726
  in cycloadditions, 723
  in Fischer indole synthesis, 844
  in formylations, 417
  in Friedel-Crafts alkylation, 407
  in haloalkylation, 424
  in Hoesch synthesis, 424
Zinc-copper in Simmons-Smith procedure, 648
Zinc cyanide, 417
Zinc ions in hydration of alkynes, 583
Zirconium chloride, 407
Zucker-Hammett relationship, 225, 566
Z-values of solvents, 297

DATE DUE

NOV 4 '86
DEC 14 '87
NOV 26 '89
JAN 2 '90
MAR 26 '90
JAN 8 '91
MAR 19 '92
OCT 11 '92
DEC 11 95
9269

261-2500

Printed in USA

ADVANCED ORGANIC CHEMISTRY: REACTIONS, M
QD 251 M19

A17900 678953

QD 251 .M19

March, Jerry

Advanced organic chemistry:
reactions, mechanisms, and
structure

A17900678953